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COMPLETE TRANSPOSITION OF THE GREAT VESSELS

A TECHNIQUE FOR INTRACARDIAC CORRECTION

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IN THE anomaly of complete transposition of the great vessels the aorta arises from the right or anterior ventricle and the pulmonary artery from the left or posterior ventricle. Thus, blood ejected from the left ventricle passes through the pulmonary circulation and returns to the left atrium while blood leaving the right ventricle courses through the systemic circulation and returns to the right atrium. This condition is incompatible with life unless some type of communication exists between systemic and pulmonic circulation. In practically all cases there is a patent foramen ovale, in about one-half of the cases a ventricular septal defect exists, and a patent ductus arteriosus or an atrial septal defect is present in about one-third of the cases.

The condition was formerly considered to be uncommon and hence, of little clinical importance; however, Gardiner and Keith[6] have reported complete transposition to occur in 6 per cent of their cases of congenital heart disease, while in the same series tetralogy of Fallot occurred in only 8 per cent.

Although at birth infants with this condition may appear to be in good condition, about one-fourth die by the end of a month and three-fourths by the end of the first year. In view of its frequency, the inherently high mortality rate and the relative ease with which the diagnosis is made, complete transposition presents a challenge to cardiovascular surgeons.

The operative procedures that have been developed for complete transposition are of 2 types, namely, palliative and corrective. In the former category, the technique of Blalock and Hanlon[4, 5, 7] for creation of an interatrial defect is outstanding for its simplicity and effectiveness as a palliative measure. Techniques for transposing the right pulmonary veins and inferior vena cava have been described by Lillehei and Varco,[9] Murphy and associates,[10] and

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Baffes.[2] Among the procedures designed to correct complete transposition of the great vessels are those of Mustard and associates[11] and Bailey.[3] These consist of restoring the aorta and pulmonary artery to their natural positions. Recently, Albert[1] has proposed the reversal of circulation within the atria by creation of baffles from the atrial septum. The use of a patch of polyvinyl sponge to retranspose the circulation within the atria has been suggested by Latson.[8] After repeated trials on experimental animals, this procedure was recently employed by us for the treatment of a clinical case of complete transposition. The patient succumbed from respiratory obstruction 12 hours following operation, having fully reacted and with a peripheral oxygen saturation of 100 per cent. This experience leads us to believe that this procedure is technically feasible and may be an effective way of completely correcting the unnatural circulatory condition.

CASE REPORT

S. V. H., a 9-month-old white male infant, was admitted to Charity Hospital in New Orleans on Dec. 2, 1956, with a history of cyanosis since birth. These episodes were fairly well controlled with morphine suppositories and a maintenance dose of digitalis. This infant was the product of a normal period of gestation and of a spontaneous delivery, with a birth weight of 9 pounds 4 ounces. On the day of delivery the child was noted to be cyanotic and was placed in oxygen. The electrocardiogram at that time was nonspecific. At the age of 7 days, he was removed from oxygen and shortly thereafter became deeply cyanotic. He was placed in oxygen again, but cyanosis, especially on crying, remained. Digitalis therapy was begun because of enlarged liver and dyspnea. Subsequently there was general improvement with lessening of cyanosis and the infant was discharged from the hospital at 5 weeks of age. At 3 months he was readmitted to the hospital for cardiac catheterization and a diagnosis of complete transposition of the great vessels and atrial septal defect was made. Arterial oxygen saturation under varying conditions was between 12 and 27 per cent except during administration of 100 per cent oxygen at rest when 48 per cent saturation was achieved. Following completion of these studies the infant was maintained on digitalis and diuretics.

Admission physical examination on Dec. 2, 1956, revealed a temperature of 101° F., pulse of 120 per minute, respirations 36 per minute, and weight of 13 pounds 14 ounces. The child appeared chronically ill, poorly developed for his age, and exhibited generalized cyanosis with clubbing of fingers and toes.

There was a soft blowing precordial systolic murmur. The liver edge was palpable at the right costal margin.

Laboratory data were as follows: hemoglobin 18.5 Gm., erythrocytes 6.31, leukocytes 9,100, urinalysis normal; x-rays of the chest revealed slight cardiac enlargement and increased vascularity of the lung fields. On Dec. 3, 1956, the child manifested rhythmic clonic contractions in the right upper extremity, a suggestive left facial weakness, and, subsequently, transient flaccidity of the right upper extremity. It appeared that he had suffered a cerebral vascular accident due to polycythemia and/or anoxia and that an attempt to correct the cardiac malformation should be made immediately.

On Dec. 4, 1956, under general anesthesia (cyclopropane, ether, and oxygen), a bilateral thoracotomy was performed through the fourth intercostal spaces, transecting the sternum. The pericardium was incised widely, exposing the heart and origin of the great vessels. The aorta was observed to arise from the anterior ventricle and the pulmonary artery from the posterior ventricle. Digital exploration of the atrial septum via the right auricular appendage confirmed the presence of an atrial septal defect. The patient was given 21 mg. of heparin intravenously and then catheters were introduced into the superior and inferior venae cavae through the right atrial appendage. The right common femoral artery was

exposed through a small incision in the groin and a catheter was inserted and directed toward the heart for arterial inflow. By utilizing a modified DeWall bubble-oxygenator, effective exclusion of the heart and lungs was achieved and an increase in peripheral oxygen saturation noted. The aorta was occluded just above the coronary ostia and 5 c.c. of a mixture of oxygenated blood and 25 per cent potassium citrate was injected and complete cardiac standstill achieved. The right atrium was incised and a lacework type of defect was found in the region of the fossa ovalis (Fig. 1). The atrial septum was completely excised exposing the orifices of the pulmonary veins. A previously prepared

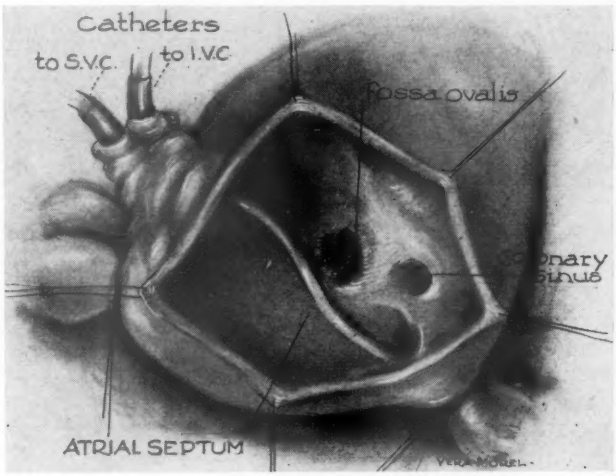


Fig. 1.—Drawing made at operation to demonstrate the atrial septal defect in the region of the fossa ovalis and caval catheters in place for extracorporeal circulation.

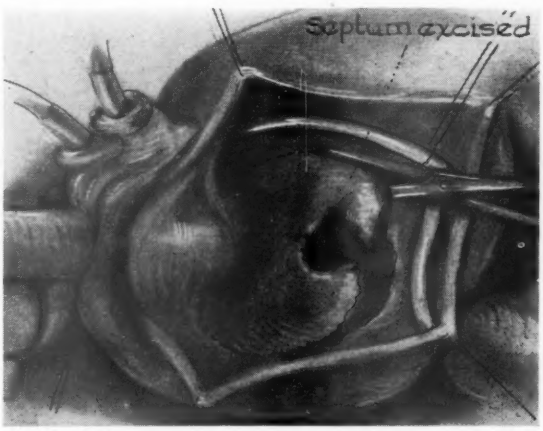
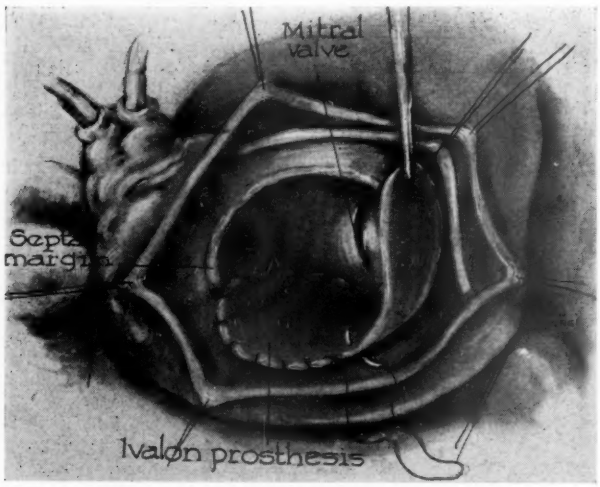
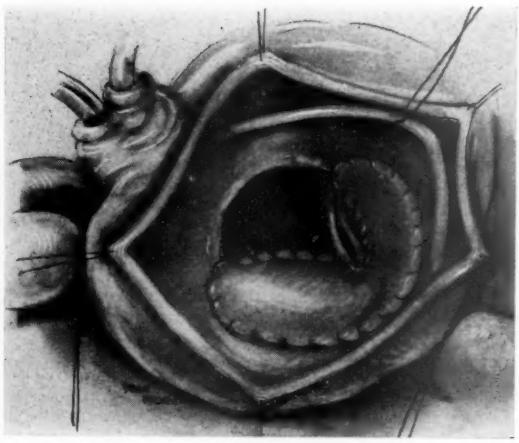


Fig. 2.—The atrial septum is completely excised thus creating a common atrial chamber.

prosthesis of polyvinyl sponge, roughly kidney-shaped in contour, was then sutured into place in such a way as to shunt blood from the orifices of the pulmonary veins through the tricuspid valve into the systemic ventricle and the caval return across the prosthesis into the mitral valve and pulmonary ventricle (Fig. 3). In suturing the prosthesis in place, it was necessary to partially compromise the orifice of the coronary sinus and divert the coronary sinus flow into the systemic chambers. The incision in the right atrium was partially closed, the clamp on the aorta was released allowing coronary perfusion to take place, and after several seconds of coronary flow the remainder of the atrial incision was



A.



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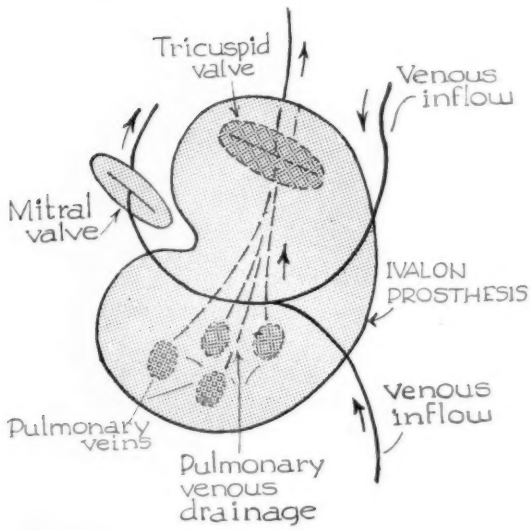

C.

Fig. 3.—*A*, A prosthesis of polyvinyl sponge (Ivalon) is sutured over the orifices of the pulmonary veins and *B*, over the tricuspid valve. *C*, The intracardiac shunt is shown diagrammatically. Pulmonary venous blood drains beneath the prosthesis into the tricuspid valve while caval return is shunted across the prosthesis into the mitral valve.

excluded in a noncrushing clamp. Cardiac activity began almost immediately and persisted. The remainder of the incision in the atrium was then closed. Perfusion lasted for 54 minutes and cardiac standstill for 35 minutes. There was a measured blood loss of 845 c.c. virtually all of it from the coronary sinus and cardiac chambers; this was replaced during perfusion. The patient was weaned from the pump over a 4-minute period while inflation of the lungs was begun. The heart was carefully observed for an additional period, hemostasis secured, and then the caval catheters were removed. The auricular appendage was ligated and the pericardium loosely approximated. An indwelling catheter was placed into each pleural space and brought out through stab wounds. The incision in the chest wall was closed in the usual manner. At the end of the procedure the patient's color was good and a sample of blood from the left femoral artery revealed 100 per cent oxygen saturation. The child was moved to the recovery room where he regained consciousness relatively early and appeared to have tolerated the procedure quite well. He seemed cognizant of his surroundings and exhibited moderate restlessness. Approximately 8 hours after operation it was noted that he was breathing with difficulty and his nail beds were slightly cyanotic. The respiratory distress progressed during the ensuing hours and ended in increasing cyanosis and cardiac standstill. The operative wound was reopened and rhythmic cardiac compression started immediately. An endotracheal tube was passed and attached to a Jefferson ventilator. Cardiac action resumed after a period of 11 minutes. The incision was again closed and at this time the child's color was good. However, consciousness was not regained although a corneal reflex was present. Approximately 3 hours later the child developed progressive cyanosis and bradycardia. His condition worsened and he succumbed approximately 12 hours following operation.

At autopsy there was a moderate amount of thick mucoid material in the trachea and main bronchi and atelectasis of the right lower lobe. The remainder of the lungs was relatively normal in appearance and there was no evidence of pulmonary edema. The prosthesis itself was ideally placed, offering no impedance to caval return or left ventricular filling and apparently shunting oxygenated blood into the systemic ventricle effectively. Death was attributed to respiratory failure which in turn was due to bronchial obstruction by secretions and impaired ventilatory effort secondary to bilateral thoracotomy.

CONCLUSIONS

Cardiopulmonary bypass in infants is associated with a high mortality irrespective of the underlying congenital disorder or the type of corrective procedure employed. In many instances death occurs within 12 to 24 hours after operation and appears to be a result of respiratory complications. For this reason it is unlikely that death in the case described above was a direct result of the technique utilized to retranspose the circulation. Subsequent experience with this technique in the experimental animal has made possible the elimination of several time-consuming maneuvers reducing thereby the period of perfusion and open cardiotomy to less than 30 minutes. In addition, the procedure can be readily accomplished through a right anterior thoracotomy without transecting the sternum, thus minimizing interference with ventilatory function.

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SUPERIOR VENA CAVAL REPLACEMENT

II. Successful Use of a Pedicle Tube Created From Right Atrium and Appendage

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SUPERIOR vena caval obstruction may be produced by a variety of intrathoracic disorders including malignant neoplasms, chronic fibrosing mediastinitis, and aortic aneurysms. While no more than palliation can be hoped for in some of the disorders, long-term relief of symptoms may be sought in others.

Unfortunately, much of the clinical and laboratory work on superior vena caval replacement has been discouraging. Experimental retention of graft patency has been disappointing when aortic homografts, caval homografts, and synthetic vascular prostheses have been employed. Kay[5] discovered that only 30 per cent of caval homografts retained their patency when used for caval replacement in dogs. Similar results in dogs were experienced by DeBakey[1] when aortic homografts were used. Gerbode[3] observed thrombosis or gradual fibrosis in all of 25 aortic homografts used to replace resected segments of superior vena cava. Deterling and Bhonslay[2] found Ivalon tubes to be uniformly unsuccessful and their results with tubes of nylon and of Dacron were little better. Venous autografts constructed from peripheral veins by the panel technique also functioned poorly in their hands. The unsuitability of free tubes of pericardium for caval replacement has been described recently.[6]

One of the more encouraging experimental studies was published in 1949 by Gerbode, Yee, and Rundle.[4] They anastomosed the superior vena cava, transected just above its junction with the azygos vein, to the right auricular appendage in 10 dogs. The anastomosis remained patent in 7 animals. In 3 animals, complete vena caval occlusion by thrombus formation occurred following operation. However, in each of these 3 dogs, a technical explanation could be found for the anastomotic failure.

A major limitation to the usefulness of right atrial appendage for caval replacement involves the relatively short segment of superior vena cava which can be replaced in this manner. For this reason, it has seemed desirable to report the following study in which we have attempted to expand the scope of superior vena caval replacement with autogenous atrial tissue through the use of a pedicle tube created from the right atrium and atrial appendage.

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MATERIAL AND METHODS

Healthy mongrel dogs were used. The weight of the dogs ranged from 9 to 27 Kg. A mixture of oxygen and ether, delivered through an endotracheal tube by means of a mechanical respirator, was employed for anesthesia following induction with intravenous Pentothal. A right third intercostal space thoracotomy incision was used.

When the right chest was opened, the superior vena cava was dissected free from surrounding structures and the pericardium was opened. While the right atrial appendage was controlled with a smooth forceps, 2 straight Potts coarctation clamps were applied, side by side, to the wall of the right atrium just above the right coronary artery and along the root of the aorta (Fig. 1). The atrial wall was incised between the 2 Potts clamps and a pedicle tube of atrium and appendage was created. Both divided segments of atrial wall were closed with a continuous suture of 4-0 arterial silk. On completion of the suture, the clamps on the atrium were removed. An additional length varying from 3 to 5 cm., accordingly, was added to the atrial appendage.

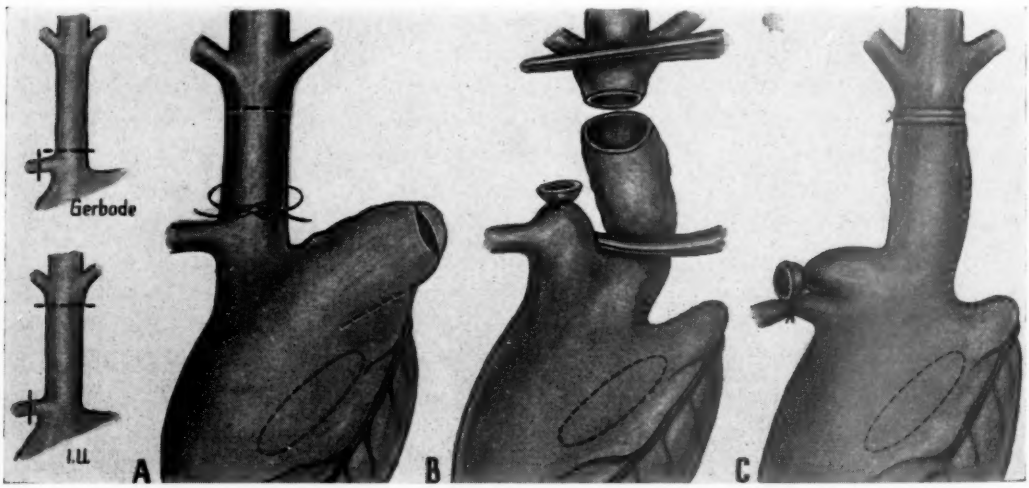

Fig. 1.—Drawings illustrating the technique for creating a pedicle tube from right atrium and atrial appendage. The area of atrial division and the anterior incision in the atrial appendage are shown in *A*. The completed atriocaval anastomosis and the appearance of the atrial tube are pictured in *C*. The proximal end of the divided vena cava has been sutured to the chest wall in the region of the azygos vein in order to straighten out the atrial tube. The smaller figures on the left compare the extent of superior vena caval replacement possible by simple atriocaval anastomosis to the atrial appendage as described by Gerbode, Yee, and Rundle[4] with the use of the tube made from atrium and appendage (I.U.).

Occasionally some arrhythmia developed when the Potts clamps were applied to the atrial wall. When this occurred, sinoauricular node blockage with 5 to 8 c.c. of Xylocaine was carried out.[7] The effect was immediate. The clamps then could be applied safely and the heart generally remained regular and calm throughout the remainder of the procedure.

The superior vena cava and the right costocervical-vertebral venous trunk were occluded with a Potts coarctation clamp, the blades of which were covered with sheaths of filter nylon fabic. These sheaths greatly facilitated the

gentle handling of the vena cava without slippage during division and subsequent anastomosis. The superior vena cava then was divided just below the origin of the right costocervical-vertebral venous trunk. The proximal end of the divided vena cava was doubly ligated and transfixed. The base of the newly formed pedicle tube of atrium and atrial appendage was occluded with a curved Potts clamp. The anterior surface of the tip of the appendage was incised to create an opening of adequate size for anastomosis with the distal end of the divided superior vena cava. At times, it was necessary to excise one or more trabeculae to obtain a satisfactory opening. The anastomosis was carried out with a continuous everting mattress suture of 5-0 arterial silk. The open end of the vena cava and the atrial appendage were irrigated intermittently during the anastomosis with normal salt solution containing a small amount of heparin.

In the first few animals, the tip of the atrial appendage was amputated and the open end was used for anastomosis. However, it was found that a disproportionate amount of traction regularly occurred at the posterior anastomotic suture line. For this reason, the anterior incision at the tip of the appendage was employed to prevent this traction and provide more length for the posterior aspect of the pedicle tube of atrium and appendage.

When the anastomosis was completed, the atrial clamp was removed and possible bleeding points along the anastomosis were investigated. Bleeding at the suture line seldom was a problem. When it did occur, a single interrupted 5-0 arterial silk suture generally was adequate. The occluding superior vena caval clamp then was released and the azygos vein was ligated. The proximal end of the divided and ligated superior vena cava was sutured to the chest wall in the region of the ligated azygos vein. This served to bring the atrial tube into the approximate anatomic position previously occupied by the replaced proximal segment of the superior vena cava and aided in preventing narrowing or kinking at the base of the atrial tube. The creation of the atrial tube did not appear to compromise right atrial or tricuspid valvular function. Electrocardiographic tracings were made at the completion of operation in the initial 5 dogs. The tracings were regarded as being within normal limits in all. It was possible consistently to construct a pedicle atrial tube of sufficient length to replace the superior vena cava to a point just below the origin of the right costocervical-vertebral trunk.

The period of superior vena caval occlusion required to complete the anastomosis ranged from 21 to 40 minutes and averaged 25 minutes. The atrial tube and anastomosis appeared to be patent in all of the animals at the time of thoracotomy closure.

The immediate function of the atrial tube and anastomosis and the adequacy of the lumen at the anastomotic site appeared to be excellent in 20 dogs, fair in 3, and poor in 1. The immediate result was regarded as only fair when there was some significant degree of narrowing at the point of atriocaval anastomosis. In one animal, Dog 20, a tear in the posterior wall of the atrium at the base of the atrial tube occurred at the completion of the anastomosis.

It was necessary to place several interrupted sutures blindly to control the loss of blood. Although the atrial tube remained open and free from thrombosis, the sutures did produce a rather marked narrowing of the lumen of the tube at its base. For this reason, the immediate result was regarded as poor.

No effort was made to close the mediastinal pleura over the atrial tube. The chest wall was closed in layers and a catheter which was left in the chest during the closure was aspirated and withdrawn.

RESULTS

The operation for superior vena caval replacement with a pedicle tube of atrium was carried out as described in 24 dogs. All of the animals survived operation.

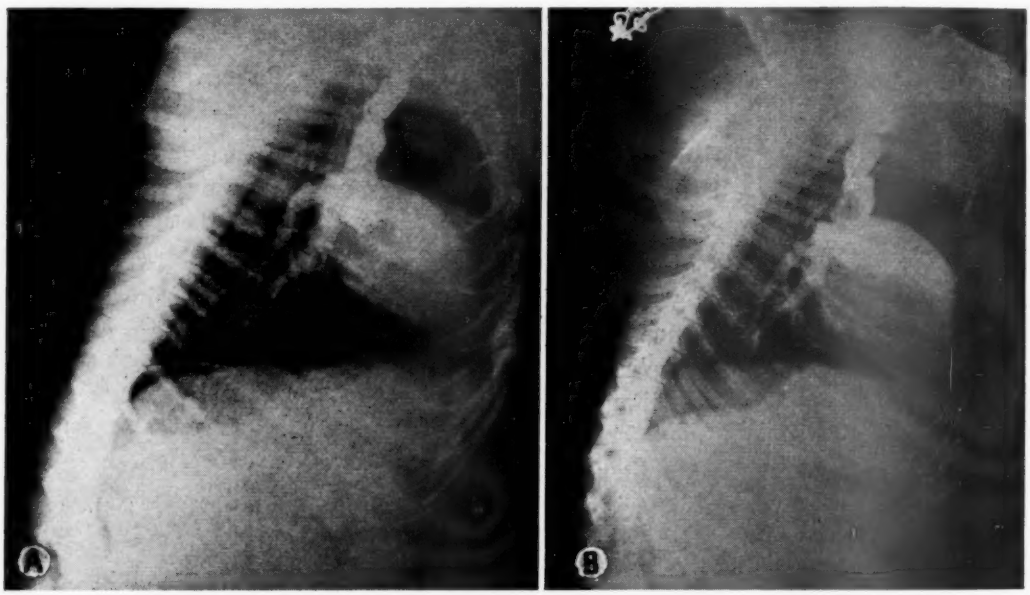

Fig. 2.—Representative cavograms showing good atrial tube and atriocaval anastomotic patency and function in Dog 21 (*A*) and Dog 22 (*B*) 4 months after operation.

The patency and function of the atrial tube and the atriocaval anastomosis were investigated following operation by cavograms in all but one animal. This animal, Dog 23, died 2 days following operation and was found on postmortem examination to have a patent and satisfactory appearing atrial tube and anastomosis. Cavograms were made under Pentothal anesthesia with an endotracheal tube in place. Fifteen cubic centimeters of 70 per cent Urokon were injected rapidly through a No. 15 gauge needle into a front leg vein. Roentgenograms were taken immediately upon completion of the injection. Initial cavograms were made in 23 dogs from 3 hours to 113 days after operation. In all of them the atrial tube and the anastomosis were shown to be patent (Fig. 2). In the animal, Dog 20, in which a poor immediate result had been observed at the time of operation, the anastomosis had remained patent. However, considerable narrowing was noted on this animal's cavogram in the

region of the proximal end of the atrial tube. This was the point at which an atrial tear had occurred necessitating the blind placement of several sutures in the posterior atrial wall.

Second and third cavograms were taken in 12 animals from 8 to 170 days following operation. Retention of atrial tube and atriocaval anastomotic patency was demonstrated in all but one of them. The use of the cavogram

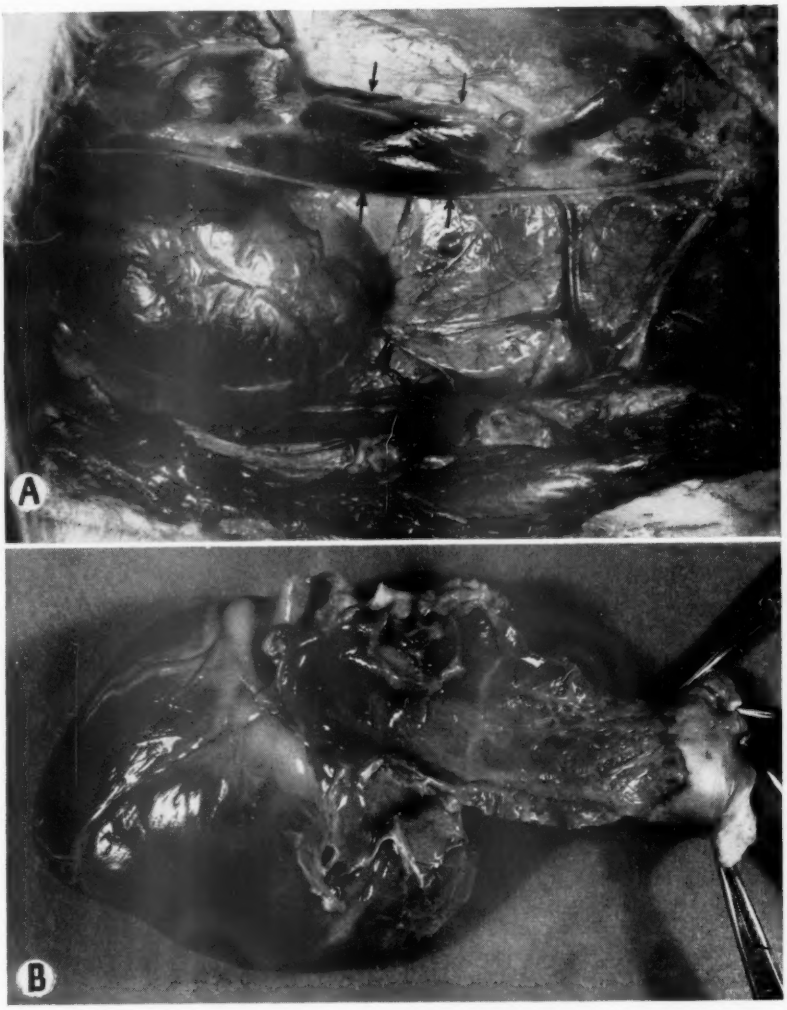

Fig. 3.—Photographs showing appearance of atrial tube and atriocaval anastomosis (arrows) 4 months after operation in Dog 8 (*A*) with the right chest opened at sacrifice and (*B*) with the heart removed and the atrial tube and superior vena cava opened. The atrial tube and the anastomosis are widely patent and free of thrombus formation. The suture line at the anastomosis is well endothelized.

is well suited for repeated postoperative evaluation of atrial tube and anastomotic patency without the necessity of sacrificing the animal. For this reason, it is possible to save a number of animals for long-term studies without interfering with statistical study of the shorter term results.

Five animals died from 2 to 60 days following operation. Pneumonia appeared to be the cause of death in 2 animals. Atelectasis was regarded as the

cause of death in 2, complicated by the presence of hemothorax in one of them. No clear cause of death could be found in one animal. The atrial tube and the atriocaval anastomsis were found to be patent and free of thrombus formation in all of them.

Nine additional animals were sacrificed from 8 to 150 days after operation. In all but one of them, the atrial tube and the anastomosis were patent and free of thrombus formation (Figs. 3 and 4). Obstruction of the atrial tube

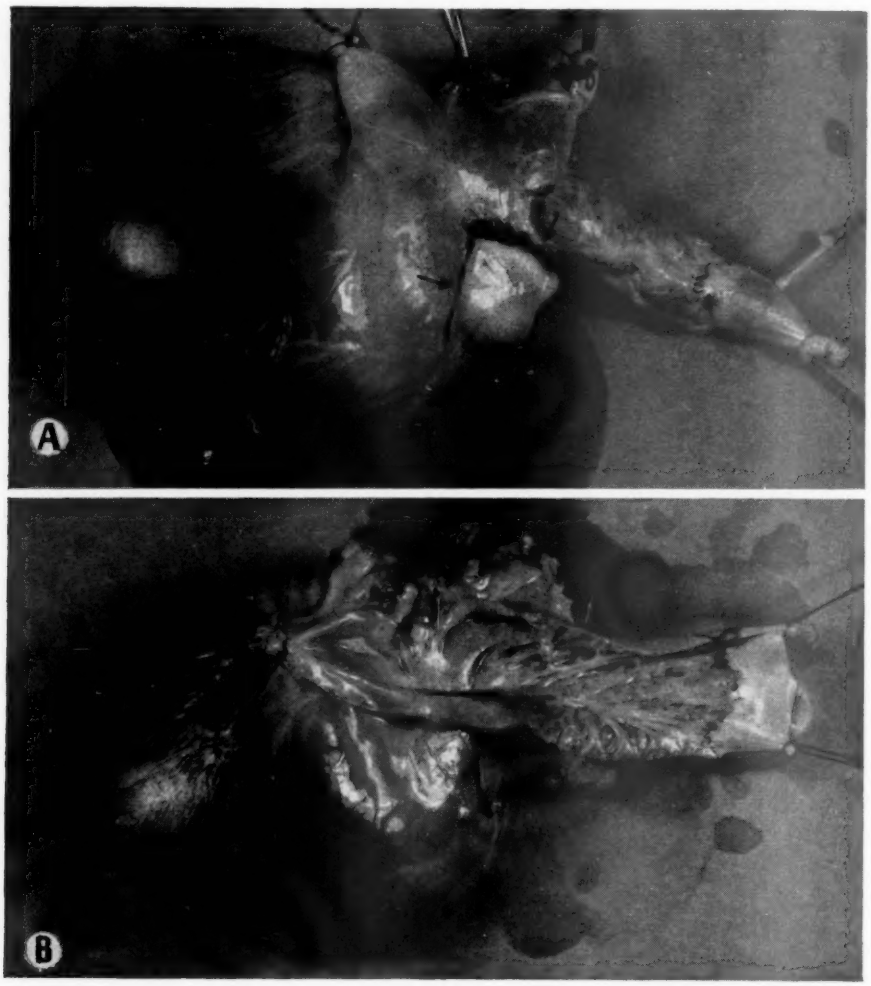

Fig. 4.—Photographs of the heart and atrial tube in Dog 19, 4 months following operation. In *A*, the atrial suture lines (arrows) demonstrate the extent of atrial division utilized to form the atrial tube. The tube and anastomosis are opened in *B* to show their patency and freedom from thrombosis. The anastomotic suture line is well endothelized.

near the anastomosis was observed in Dog 16 on sacrifice 137 days after operation. A funnel-shaped obstruction had been produced by scarring which had resulted from the inadvertent placement of a suture through an adjacent atrial trabecula during the atriocaval anastomosis. The anastomosis otherwise was patent and the suture line was well endothelized. There was no evidence of thrombus formation. The occurrence of some constriction near the atriocaval

anastomosis had been observed in this animal at the time of operation. Although the initial 2 cavograms had shown patency of the atrial tube, occlusion was found on the third cavogram which was made 4 days prior to sacrifice. In Dog 20, previously mentioned, there was clinical evidence of superior vena caval obstruction with an accumulation of clear fluid in the chest. It was found that the base of the atrial tube, where sutures had been placed blindly at operation to close a tear, had been almost completely closed by the sutures. Only a small, pinpoint opening remained. Despite this obstruction, both the atriocaval anastomosis and the remainder of the atrial tube had remained widely patent and completely free of thrombus formation.

No evidence of progressive suture line constriction was encountered in any of the animals studied at necropsy. Microscopic examination of the atrial tubes and the atriocaval anastomosis revealed satisfactory endothelization of the suture lines in all of the animals studied. There was no microscopic evidence of thrombus formation.

Nine animals are known to be alive. In none of them is there clinical evidence of superior vena caval obstruction. These clinical observations of continued atrial tube and atriocaval anastomotic patency have been confirmed by repeated cavograms. One other animal was lost from the colony subsequent to cavogram demonstration of the atrial tube and anastomosis patency 63 days following operation.

Thus, 14 of the animals are dead, 1 is lost, and 9 are living. All have been studied by cavograms, autopsy, or both. The duration of caval replacement at the time of cavogram or autopsy study of the tube and anastomosis has exceeded 4 months in 14 of the 24 animals. The atrial tube and anastomosis were patent in 23 of the 24 dogs. Occlusion in the one animal resulted from faulty anastomotic suture placement rather than from thrombosis. Although partial or complete occlusion of the atrial tube occurred through technical error in 2 animals, the atrial tube and atriocaval anastomosis in both remained free of thrombus formation. The suture lines in all animals were found to be well endothelized. Thrombus formation was not encountered.

DISCUSSION

The published clinical and laboratory experience with venous replacement, principally vena caval replacement, indicates clearly that the margin of safety for successful function is considerably less than that encountered in artery grafting. Most of the vascular substitutes which have found to be successful in arterial by-pass or replacement have failed to function satisfactorily as venous grafts. The use of both homografts and vascular prostheses has been disappointing.

Atriocaval anastomosis to by-pass low superior vena caval obstruction has met with more success. The work of Gerbode and his associates[4] has demonstrated that one may expect the majority of atriocaval anastomoses to remain open. Two of their 3 failures occurred in animals in which the atriocaval anastomosis was carried out as a secondary procedure and in the presence of

pre-existing partial or complete thrombotic occlusion of the superior vena cava. The other failure, in this group of 10 dogs, occurred in an animal in which an additional suture for bleeding had produced some suture line twisting and narrowing. More recently, Gerbode has reported on some of the long-term follow-up experiences with these anastomoses. He had followed some of the animals with atriocaval shunts more than 5 years. In one animal in which the superior vena cava was moved over to the atrial appendage, the anastomosis appeared smooth after 2½ years. He concluded that atriocaval shunts which remain open beyond the immediate healing stages will most likely stay open indefinitely.

Unfortunately, the length of proximal superior vena cava which can be replaced by simple anastomosis between the vena cava and the atrial appendage is limited. However, the scope of superior vena caval replacement or by-pass by means of atriocaval anastomosis may be increased significantly through the use of a pedicle vascular tube created from the right atrium and atrial appendage. The safety of this procedure is indicated by the immediate survival of all of the animals in which this operation was undertaken. The use of sinoauricular node blockade appeared to be of value in some animals. No apparent impairment in venous return or in cardiac function was noted at the time of operation, and none of the deaths which occurred after operation appeared to be due to cardiovascular causes.

The results of this study confirm the observations of Gerbode and his associates[4] concerning the retention of patency of atriocaval anastomoses and expand this experience to include pedicle tubes made from atrium and atrial appendage. This method would appear to satisfy some of the more rigid theoretic criteria for superior vena caval replacement. Available living autogenous endothelized vascular tissue on a pedicle is used. The retention of atrial tube and atriocaval anastomotic patency in 23 of 24 animals, observed up to 6 months after operation, is convincing. The patency of the tube and anastomosis and their freedom from thrombus formation in Dog 20, despite the almost complete accidentally produced occlusion of the base of the atrial tube is rather remarkable. Only in Dog 16 did occlusion occur. This was observed on cavogram 4 months following operation and was shown on post-mortem examination to be due to faulty anastomotic suture placement in one area rather than to thrombosis.

SUMMARY

A method for superior vena caval replacement or by-pass through the use of a pedicle tube made from the right atrium and right atrial appendage is described. The operation was carried out in 24 consecutive dogs without immediate mortality. Atrial tube and atriocaval anastomotic patency and their freedom from thrombus formation were investigated by cavograms, necropsy, or both from 3 hours to 6 months after operation. In 23 of the 24 dogs operated upon, the atrial tube and the atriocaval anastomosis remained patent. The one failure was due to a technical error. In all of the animals studied at

post-mortem examination, the tube and anastomosis appeared smooth and the suture lines were well endothelized. There was no evidence of thrombus formation. The results of this study suggest the suitability of this method for extending the scope of superior vena caval replacement through atriocaval anastomosis.

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COMPLICATIONS OF AORTOGRAPHY

Factors Influencing Renal Function Following Aortography With 70 Per Cent Urokon

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SINCE its introduction in 1929 by dos Santos and associates,[3] translumbar aortography has become a very useful diagnostic medium in the treatment of certain vascular and renal abnormalities. The usefulness and popularity of this procedure have increased tremendously with the recent lively interest in aortic disease, and the ultimate extent of its application will depend largely upon the frequency and significance of its complications. The relative safety of aortography is evident by the numerous reported applications without incident and the general extent to which it is now being applied. A review of the literature appears to confirm the low incidence of complications; however, the procedure is not entirely harmless and certain difficulties may result from its use. The most common significant complication of aortography is renal damage and this, therefore, constitutes the major risk of the procedure.[1, 6] Clinical experience and an analysis of the cases in which renal damage occurred suggest that certain factors may predispose to the development of renal complications. These seem to be concerned primarily with the effects of the contrast material on the kidneys. In order to minimize or eliminate this complication, it is necessary to understand the effects of the contrast medium upon renal function. With this objective, an experiment was undertaken to study renal function following aortography with the following variables: (1) dosage of contrast medium, (2) the site of injection, and (3) the presence of infrarenal occlusion.

METHODS AND MATERIALS

Experimental.—Fifty-one female dogs, varying in weight from 8.0 to 23.5 kilograms were divided into 3 groups, each consisting of 3 subgroups (A, B, and C). Determinations were recorded of the blood pressure, glomerular filtration rate, renal blood flow, and hematocrit. Group I consisted of 25 animals in which the immediate effect of aortography was observed (Table I). Both ureters were cannulated for the collection of urine, and observations on hemodynamics were

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made on each kidney independently. Following suitable control observations, 70 per cent Urokon sodium was injected into the aorta (subgroups IA and IB) or into one renal artery (subgroup IC). Observations on renal function were made immediately and for 2 hours after injections of the Urokon.

Group II consisted of 26 animals in which the persisting effect of aortography was observed 3 to 5 days following injection of the contrast material (Table II). In these studies, control observations were made with urine collected by an indwelling urethral catheter. The 70 per cent Urokon sodium was then injected into the aorta (subgroups IIA and IIB) or into the renal artery (subgroup IIC). Three to five days following injection, both ureters were cannulated for the collection of urine, and observations on hemodynamics were made separately on each kidney. In this group one half of control values for both kidneys was used for comparison with follow-up values for the individual kidney; thus, it was assumed that prior to injection of Urokon the blood flow through the right and left kidneys was approximately equal. The validity of this assumption is supported by the observations made on the dogs in Group I when glomerular filtration rate and renal blood flow were determined in the kidneys separately (right and left) during the control period and prior to injection of Urokon (Table I).

Subgroups IA and IIA consisted of animals in which 0.35 ml. per kilogram of 70 per cent Urokon sodium was injected rapidly (approximately one second) through a special, short bevel, No. 18 gauge needle into the suprarenal portion of the abdominal aorta without aortic occlusion. The angling and size of the needle and the rate of injection were kept constant in all animals and simulated the manner used in human aortography, except that the aorta was approached by the retroperitoneal rather than the percutaneous route. The needle hole was compressed with gauze to control postpuncture bleeding, and the site was inspected for oozing prior to closure of the wound. The same procedure was employed in subgroups IB and IIB except that the aorta was occluded below the renal arteries with a Potts nonerushing artery clamp. The clamp was applied prior to injection and removed 30 seconds after completion of the injection. In subgroups IC and IIC 0.35 ml. per kilogram of 70 per cent Urokon was injected rapidly into the left renal artery.

Group III consisted of 15 dogs in which 1.05 ml. per kilogram of 70 per cent Urokon sodium was injected into the aorta similar to the procedure in Group II in which 0.35 ml. per kilogram was used. The aorta was unoccluded in 8 dogs, and in the remaining 7 animals the aorta was temporarily occluded immediately below the origin of the renal arteries.

All dogs were given 40 ml. per kilogram of water by mouth prior to the renal function studies. Forty-five minutes later they were anesthetized with pentobarbital (30 mg. per kilogram of body weight) intravenously. Mean blood pressure was measured by a damped mercury manometer connected through a manifold to an indwelling femoral artery needle. Creatinine was used to measure glomerular filtration rate and para-aminohippurate was used to measure renal plasma flow. Renal blood flow was determined from renal plasma flow and the

TABLE I. ACUTE RENAL HEMODYNAMIC RESPONSE TO INTRA-ARTERIAL INJECTION OF UROKON IN DOGS

DOG NO.	MEAN BLOOD PRESSURE MM. HG			GLOMERULAR FILTRATION RATE (ML./MIN.)						RENAL BLOOD FLOW (ML./MIN.)						HEMATOCRIT			BODY WEIGHT (KG.)
				C		D_1		D_2		C		D_1		D_2					
	C	D_1	D_2	R	L	R	L	R	L	R	L	R	L	R	L	C	D_1	D_2	
Subgroup 1A—Effects of the injection of 0.35 ml. per kilogram of 70 per cent Urokon sodium into the suprarenal portion of the unoccluded abdominal aorta																			
1	114	103	108	23	25	19	17	20	22	124	114	65	60	70	85	42	45	39	17.0
2	114	75	75	19	19	2	1	7	15	94	94	6	6	33	50	38	36	36	17.0
3	133	119	124	14	14	9	8	11	6	81	83	63	74	42	35	53	57	57	16.0
4	131	129	127	28	32	17	29	25	27	137	144	56	107	96	100	43	43	43	10.5
5	120	98	123	29	22	29	10	20	18	145	100	90	58	73	77	54	52	52	18.0
6	87	51	90	16	20	7	14	14	17	78	98	15	34	40	42	35	35	35	10.0
7	147	123	124	24	24	17	18	18	21	114	112	66	66	94	98	49	50	46	8.0
8	128	123	97	29	23	29	28	27	38	140	152	90	85	108	114	48	52	51	13.0
Mean	122	103	109	23	22	16	16	18	21	114	112	56	61	70	75	44	46	45	
Per cent of control		84	89			70	73	78	95			49	54	61	67		105	102	
P value* <		0.01	0.10			.05	.05	.01	.10			.001	.001	.001	.001		.10	.50	
Subgroup 1B—Effects of the injection of 0.35 ml. per kilogram of 70 per cent Urokon sodium into the suprarenal portion of the occluded abdominal aorta																			
1	90	97	100	34	22	18	22	8	11	154	117	105	118	49	74	59	60	61	16.4
2	99	83	99	26	25	18	17	11	13	139	130	54	48	33	54	43	39	39	13.9
3	88	105	68	15	15	4	3	1	1	154	166	27	18	3	3	59	55	40	13.0
4	118	95	90	12	16	5	9	5	4	36	76	26	37	25	20	34	38	36	15.2
5	75	54	38	17	17	5	4	1	5	100	91	25	22	8	28	45	45	40	10.0
6	87	130	125	28	29	23	21	14	13	100	116	81	71	105	88	45	42	43	15.3
7	102	112	117	34	31	16	21	24	32	206	204	51	60	91	87	49	47	47	12.0
8	105	124	126	50	35	2	8	1	10	240	236	7	42	3	68	55	40	60	17.0
9	102	122	134	9	8	7	4	10	2	60	42	29	11	31	13	43	45	45	18.0
10	126	110	120	23	12	23	7	17	12	159	122	213	53	109	91	51	53	55	11.0
11	129	98	97	13	12	12	12	15	21	153	122	97	70	99	75	42	40	32	9.5
12	123	121	128	30	28	26	27	29	27	138	145	84	84	101	96	44	31	32	15.0
13	108	98	96	30	27	16	1	25	8	146	180	54	5	85	26	44	41	32	15.0
Mean	104	104	103	25	21	13	12	12	12	137	134	66	49	57	56	47	44	43	
Per cent of control		100	99			52	57	48	57			48	37	42	42		94	91	
P value* <		.50	.50			.01	.01	.01	.01			.01	.001	.01	.001		.10	.10	

Subgroup IC—Immediate effects of the injection of 0.35 ml. per kilogram of 70 per cent Urokon sodium into the left renal artery																
1	115	130	131	32	31	23	5	32	1	133	127	63	14	95	11	37	37	34	16.0
2	74	91	97	21	29	12	5	17	3	160	170	47	19	60	13	60	53	53	15.2
3	135	184	126	27	28	17	4	17	12	165	175	92	40	79	54	48	48	52	14.5
4	141	169	129	34	35	20	10	25	12	138	145	102	36	81	50	40	56	52	21.5
Mean	116	144	121	29	31	18	6	23	7	149	154	76	27	79	32	46	49	48	
Per cent of control		124	104			62	19	79	23			51	18	53	21		107	104	
P value* <		.01	.50			.01	.001	.10	.01			.05	.001	.05	.01		.50	.50	

C = Control observations, average of 3- to 10-minute periods.

D_1 = Observations immediately following injection, average of 2- to 10-minute periods.

D_2 = Observations 2 hours following injection, average of 2- to 10-minute periods.

R = Observations on the right kidney.

L = Observations on the left kidney.

$$* = t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$$

TABLE II. CHANGES IN RENAL HEMODYNAMICS 3 TO 5 DAYS FOLLOWING INTRA-ARTERIAL INJECTION OF UROKON IN DOGS

DOG NO.	MEAN BLOOD PRESSURE (MM. HG.)		GLOMERULAR FILTRATION RATE (C.C./MIN.)			RENAL BLOOD FLOW (C.C./MIN.)			HEMATOCRIT		BODY WEIGHT (KG.)
				D			D				
	C	D	½ C	R	L	½ C	R	L	C	D	
Group IIA—Changes following the injection of 0.35 ml per kilogram of 70 per cent Urokon sodium into the suprarenal portion of the unoccluded abdominal aorta											
1	110	89	20	14	4	108	47	18	48	34	12.1
2	92	94	18	17	10	115	80	51	45	30	11.0
3	103	70	25	17	25	186	109	183	44	35	9.0
4	124	95	18	12	15	83	99	93	40	32	9.0
5	97	96	18	16	17	70	92	98	40	40	12.0
6	102	65	48	35	32	296	268	287	47	47	16.0
7	97	102	18	16	9	62	103	121	32	38	12.0
Mean	104	87	24	18	16	131	114	122	42	37	
Per cent of control		84		75	67		87	93		88	
P value <		.10		.05	.05		.40	.50		.10	
Group IIB—Changes following the injection of 0.35 ml. per kilogram of 70 per cent Urokon sodium into the suprarenal portion of the occluded abdominal aorta											
1	65	106	26	13	1	140	77	3	40	31	16.0
2	117	77	17	17	18	117	100	105	48	38	13.0
3	99	115	38	35	39	194	192	219	38	37	15.0
4	109	119	32	37	33	116	139	144	38	36	20.0
5	90	100	45	9	27	208	62	131	40	35	17.0
6	147	127	37	24	23	222	197	288	41	40	23.0
7	94	113	23	20	25	144	102	123	39	35	12.5
8	109	51	19	5	8	86	33	72	41	40	12.0
9	87	107	29	28	34	176	208	217	49	47	15.0
10	102	89	33	38	47	233	255	238	55	60	—
Mean	102	100	30	23	26	164	137	154	43	40	
Per cent of control		98		77	87		84	94		93	
P value <		.50		.20	.40		.20	.50		.10	
Group IIC—Changes in renal hemodynamics 3 to 5 days following injection of 0.35 ml. per kilogram of 70 per cent Urokon sodium into the left renal artery											
1	92	126	33	34	3	125	181	28	40	43	13.0
2	91	120	12	16	3	88	82	12	48	35	12.1
3	101	78	19	23	12	136	218	65	45	45	11.5
4	98	108	6	3	0	72	26	0	40	38	9.0
5	74	113	17	19	8	66	73	47	38	40	9.0
6	114	92	20	23	4	157	129	24	47	51	16.0
7	104	79	17	19	3	123	139	53	40	38	11.0
8	115	69	31	27	20	174	188	138	38	34	12.0
9	115	105	32	39	3	130	180	14	37	30	16.0
Mean	100	99	21	23	6	119	135	42	41	39	
Per cent of control		99		110	29		113	35		95	
P value <		.50		.20	.001		.30	.001		.30	

C—Control observations; ½ C—Control observation for each kidney = one half the value for both kidneys.

D — Observations made 3 to 5 days after injection of Urokon.

R — Right kidney.

L — Left kidney.

hematocrit (Renal Blood Flow = $\frac{\text{Renal Plasma Flow}}{1 - \text{Hematocrit}}$). Control observations consisted of three 10-minute collection periods. This permitted comparison of the consistency of the observations for consecutive 10-minute periods, thus serving as a check on the technical accuracy. If there was excessive variation during consecutive control periods indicating a technical defect, the study was discarded. For presentation of data (Tables I and II) the averages of the observations made during the consecutive control periods were recorded as the control values. For the acute response (Group I) immediately and 2 hours following injection of the Urokon, two 10-minute collection periods were made for each period of observation. The eventual effect was determined by three 10-minute collection periods made 3 to 5 days following injection of the Urokon. Methods and techniques have been described previously.[9]

Clinical.—Eighteen men and one woman, ranging in age from 36 to 70 years, were studied before and after performance of 21 translumbar aortograms. Twenty-five to fifty ml. of 70 per cent Urokon sodium was injected into the suprarenal portion of the abdominal aorta by the percutaneous route through a special, short bevel, No. 17 gauge needle with a No. 16 gauge bore. Either an intravenous anesthetic with Pentothal sodium or a spinal anesthetic was employed. The mean blood pressure, glomerular filtration rate, renal plasma flow, hematocrit, and water and electrolyte excretion were determined. The mean blood pressure was derived from auscultatory systolic and diastolic pressures by adding one third of the pulse pressure to the diastolic pressure. Glomerular filtration rate and renal plasma flow were determined according to the inulin and para-aminohippurate clearance techniques, respectively. Renal blood flow was derived from the renal plasma flow determination. Sodium and potassium determinations were obtained with a Beckman flame photometer. Methods and techniques have been described previously.[8, 10]

The clinical observations were divided into 2 groups. In Group I (Table III) control observations consisting of three 10-minute collection periods were obtained prior to the induction of anesthesia, and two 10-minute collection periods were obtained following anesthetization. Immediately after aortography observations consisting of two-10-minute collection periods were obtained and were repeated one hour and again 2 hours later. In Group II (Table IV), which also includes most of those patients studied in Group I, three 10-minute collection periods were obtained prior to anesthetization and aortography and were repeated 24 to 48 hours later and again without anesthesia. The patients in Group II (chronic studies) were divided into subgroups A and B. Subgroup IIA consists of those patients receiving 25 to 30 ml. of 70 per cent Urokon sodium. Subgroup IIB consists of those patients receiving 35 to 50 ml. of 70 per cent Urokon sodium.

The results of both laboratory and clinical observations were subjected to statistical analysis.* All were compared with control observations. The clinical observations in Table III were compared with control observations as well as with those obtained following anesthetization.

*Statistical analysis by R. A. Seibert, Ph.D.

TABLE III. THE IMMEDIATE EFFECTS OF AORTOGRAPHY ON RENAL HEMODYNAMICS AND WATER AND ELECTROLYTE EXCRETION IN MAN

PATIENT	MEAN BLOOD PRESSURE (MM. HG)					GLOMERULAR FILTRATION RATE (C.C./MIN.)					RENAL BLOOD FLOW (C.C./MIN.)					HEMATOCRIT					70 PER CENT UROKON (C.C. INJECTED)
	C	AN	D_1	D_2	D_3	C	AN	D_1	D_2	D_3	C	AN	D_1	D_2	D_3	C	AN	D_1	D_2	D_3	
1. D. E.	103	98	99	105	93	94	77	63	68	75	1148	956	541	807	1000	46	46	46	46	46	25
2. B. J.	93	98	87	82	98	96	100	81	83	94	897	792	553	597	792	40	36	38	38	38	25
3. M. B.	84	67	67	79	82	61	46	36	45	56	638	507	216	343	426	44	42	42	44	46	49
4. B. J.	97	87	85	79	92	70	66	26	75	84	896	770	134	566	725	47	47	47	47	47	49
5. F. J.	95	82	83	92	89	72	72	37	67	82	596	543	198	454	418	47	47	36	48	43	49
6. S. M.	112	110	117	111	107	135	119	56	77	64	1524	1284	339	770	508	50	50	56	54	52	25
7. E. A.	97	80	94	103	78	119	81	89	99	134	1427	1043	580	795	984	49	49	46	43	43	50
8. M. N.	123	142	135	150	132	92	40	46	43	54	746	555	336	315	338	50	49	47	46	47	50
Mean	101	96	96	100	96	92	75	54	70	80	984	806	362	581	649	47	46	45	46	45	
Per cent of control		95	95	99	95		82	59	76	87		82	37	59	66		98	96	98	96	
P value* $<$		0.3	0.2	>0.5	0.3		0.05	0.01	0.05	0.3		0.001	0.001	0.011	0.05						
P value† $<$			>0.5	0.3	>0.5			0.05	0.5	>0.5			0.01	0.01	0.2						

TABLE III—CONT'D

PATIENT	URINE VOLUME (C.C./MIN.)					URINE SODIUM (mEq./MIN.)					URINE POTASSIUM (mEq./MIN.)					STATE OF AORTA
	C	AN	D_1	D_2	D_3	C	AN	D_1	D_2	D_3	C	AN	D_1	D_2	D_3	
1. D. E.	---	10.5	3.1	0.5	1.1	---	111	192	163	153	--	42	64	47	47	Partial occlusion
2. B. J.	1.1	0.7	1.7	1.9	2.4	163	152	255	206	186	44	37	50	56	57	Partial occlusion
3. M. B.	0.3	0.1	0.9	1.0	1.1	119	148	239	302	298	28	32	80	74	76	Partial occlusion
4. B. J.	1.0	1.4	1.6	1.4	2.3	94	108	201	283	289	30	38	37	89	108	Partial occlusion
5. F. J.	0.9	0.1	0.9	1.5	1.5	---	---	---	---	---	--	--	--	--	--	Partial occlusion
6. S. M.	6.1	0.4	1.2	1.1	1.2	286	85	143	125	89	88	45	74	66	39	Complete occlusion
7. E. A.	0.9	0.1	0.9	1.4	1.1	173	46	150	309	216	36	51	116	99	82	Partial occlusion
8. M. N.	10.4	0.3	1.5	2.2	0.4	229	28	211	203	100	43	35	78	56	63	Normal
Mean	3.0	1.7	1.5	1.4	1.4	177	97	199	227	190	45	40	71	70	67	
Per cent of control		57	50	47	47		55	112	128	107		89	158	156	149	
P value* $<$		0.3	0.5	>0.5	>0.5		0.2	>0.5	0.4	>0.5		>0.5	0.2	0.1	0.3	
P value† $<$			>0.5	>0.5	>0.5			0.001	0.01	0.05			0.05	0.01	0.05	

C = Control observations, average of 3- to 10-minute periods.
An = Observations after the induction of anesthesia, average of 2- to 10-minute periods.
D_1 = Observations immediately following aortography, average of 2- to 10-minute periods.
D_2 = Observations one hour following aortography, average of 2- to 10-minute periods.
D_3 = Observations 2 hours following aortography, average of 2- to 10-minute periods.

*$t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$, using control before anesthesia for comparison; and † using values after induction of anesthesia for comparison.

TABLE IV. ALTERATIONS IN RENAL HEMODYNAMICS 24 TO 48 HOURS FOLLOWING AORTOGRAPHY IN MAN

PATIENT	MEAN BLOOD PRESSURE (MM. HG.)			GLOMERULAR FILTRATION RATE (C.C./MIN.)			RENAL BLOOD FLOW (C.C./MIN.)			HEMATOCRIT (VOL. PER CENT)			STATE OF AORTA	PER CENT UROKON SODIUM (C.C.)
	C	DX	PER CENT CONTROL	C	DX	PER CENT CONTROL	C	DX	PER CENT CONTROL	C	DX	PER CENT CONTROL		
Group IIA. (Dose of Urokon 25 to 30 c.c.)														
1. F. L.	110	102	93	119	110	92	1235	1411	114	46	46	100	Normal	30
2. J. T.	90	90	100	52	46	88	437	367	84	41	45	110	Complete occlusion	30
3. R. C.	93	93	100	112	104	93	1298	1298	100	48	48	100	Complete occlusion	30
4. D. E.	98	90	92	77	110	143	956	1393	146	46	46	100	Partial occlusion	25
5. B. J.	93	88	95	96	90	94	897	922	103	40	37	93	Partial occlusion	25
6. B. J.	88	97	110	68	91	134	727	929	128	38	38	100	Normal graft	25
7. S. M.	112	110	98	135	118	87	1542	1265	82	50	48	96	Complete occlusion	25
8. R. O.	100	85	85	62	64	103	522	588	113	50	50	100	Normal graft	25
9. H. W.	127	110	87	65	62	95	622	994	160	42	46	110	Normal graft	25
Mean	101	96		87	88		915	1019		45	45			
Mean per cent control			96			103			114			101		
P value* <		0.010			>0.50			0.30			.50			

Group IIB.	*(Dose of Urokon 35 to 50 c.c.)*													
1. T. K.	135	130	96	67	83	124	706	721	102	47	43	91	Partial occlusion	35
2. N. K.	93	83	89	106	110	104	1175	920	78	39	36	92	Normal	35
3. R. L.	150	156	104	132	50	38†	1094	658	60	50	52	104	Normal	35
4. R. C.	123	133	108	32	27	84	277	291	105	35	42	120	Complete occlusion	40
5. R. C.	133	120	90	27	30	111	291	276	95	42	38	90	Complete occlusion	40
6. M. J.	82	80	98	87	92	106	1180	1282	109	46	43	93	Complete occlusion	40
7. B. G.	108	95	88	78	73	94	781	915	117	46	46	100	Partial occlusion	40
8. M. B.	84	75	89	61	21	34†	638	505	79	44	38	86	Partial occlusion	49
9. B. J.	97	100	103	70	43	61†	896	532	60	47	47	100	Partial occlusion	49
10. F. J.	95	99	104	72	91	126	568	743	131	47	47	100	Partial occlusion	49
11. M. N.	123	100	81	92	60	65†	746	545	73	50	40	80	Normal	50
12. J. C.	73	89	122	77	77	100	1167	637	55	55	37	67	Complete occlusion	50
Mean	108	105		75	63		793	669		46	42			
Mean per cent control			98			87			89			94		
P value* <		0.40			0.20			0.10			.20			

C = Control observations, average of 3- to 10-minute periods.
Dx = Observations 24 to 48 hours following aortography, average of 3- to 10-minute periods.

*$t = \bar{x} \sqrt{\frac{n(n-1)}{Sx^2}}$

†Renal damage due to Urokon.

RESULTS

Experimental Observations (Dogs).—In Table I (subgroup A) are tabulated the immediate effects of injection of 0.35 ml. per kilogram of 70 per cent Urokon sodium into the suprarenal portion of the abdominal aorta without aortic occlusion. Mean blood pressure fell to 84 per cent of control values immediately following injection ($p < 0.01$) and remained slightly depressed (89 per cent of control) at the end of 2 hours ($p < 0.10$). At the same time, glomerular filtration rate fell to approximately 70 per cent of control values with no significant difference between the right and left kidneys (70 per cent and 73 per cent, respectively). Renal blood flow was reduced to approximately 50 per cent of control observations. Statistically, the changes in both glomerular filtration rate and renal blood flow were significant ($p < 0.05$ and < 0.001, respectively). Two hours following injection glomerular filtration rate had risen to 78 per cent (right) and 95 per cent (left) of control values while renal blood flow had returned to only 61 per cent (right) and 67 per cent (left) of control values, a continued reduction from control values which was significant ($p < 0.001$). This continued depression in renal blood flow may have been due in part to the functional depression frequently observed with prolonged anesthesia.

The immediate effects of the intra-aortic injection of Urokon when the aorta was occluded below the renal arteries were of the same type but were somewhat more pronounced than the responses in the dogs in which the aorta was not occluded. No change occurred in mean blood pressure. Glomerular filtration rate fell to 52 per cent (right) and 57 per cent (left) of control values ($p < 0.01$) immediately following injection and at the end of 2 hours was only 48 per cent (right) and 57 per cent (left) of control values ($p < 0.01$). Renal blood flow fell to 48 per cent (right) ($p < 0.01$) and 37 per cent (left) ($p < 0.001$) of control immediately following injection and did not increase (42 per cent) ($p < 0.01$) after 2 hours. The immediate and continued depressions in renal functions were all of statistical significance. It appears that the vasoconstrictor response following injection of Urokon into the aorta with the aorta occluded (subgroup IB) was somewhat more pronounced than that observed in the dogs in which the aorta was not occluded (subgroup IA).

Injection of 0.35 ml. per kilogram of 70 per cent Urokon sodium into the left renal artery produced an immediate rise in mean blood pressure to 124 per cent of control values with return to 104 per cent of control values at the end of 2 hours. This elevation in blood pressure was statistically significant ($p < 0.01$). Glomerular filtration rate and renal blood flow fell to 19 and 18 per cent of control values, respectively, on the side of injection ($p < 0.001$). This was associated with an immediate fall in glomerular filtration rate and renal blood flow on the uninjected side to 62 and 51 per cent of control values, respectively ($p < 0.05$). The greater reduction in glomerular filtration rate and renal blood flow on the side of injection of the Urokon into the renal artery as compared with the opposite kidney (right) was also statistically significant.

The alterations in renal hemodynamics persisted for more than 2 hours after injection of the Urokon. No significant change in hematocrit occurred in the animals in Group I ($p > 0.10$).

In Table II are tabulated observations made 3 to 5 days following injection of 0.35 ml. per kilogram of 70 per cent Urokon sodium into the renal artery or the suprarenal portion of the abdominal aorta. In subgroup IIA the Urokon was injected into the suprarenal portion of the aorta without aortic occlusion. Three to five days after the Urokon was injected the mean blood pressure was found to be 84 per cent of control values ($p < 0.10$), glomerular filtration rate remained somewhat depressed at 75 per cent (right) and 67 per cent (left) of control values ($p < 0.05$), while renal blood flow had returned to 87 per cent (right) and 93 per cent (left) of control values. The residual depression in renal blood flow was not significant.

Observations made 3 to 5 days following injection of Urokon into the suprarenal portion of the abdominal aorta, during occlusion of the aorta below the renal arteries, were similar to those made on the dogs in Group 2A in which the aorta was not occluded. No change in mean blood pressure was seen. There was a slight depression in glomerular filtration rate, but this was not of statistical significance, $p < 0.20$ (right) and < 0.40 (left). Renal blood flow had returned to 84 per cent (right) and 94 per cent (left) of control values ($p < 0.20$ and > 0.50) 3 to 5 days after injection of Urokon.

In Table II (subgroup IIC) are tabulated observations made 3 to 5 days following the injection of a similar dose of 70 per cent Urokon sodium into the left renal artery. Again no significant change in mean blood pressure was seen ($p > 0.50$). On the injected side glomerular filtration rate and renal blood flow remained depressed at 29 and 35 per cent of control values, respectively, a highly significant change ($p < 0.001$). However, on the uninjected side glomerular filtration rate and renal blood flow had increased to 110 per cent ($p < 0.20$) and 113 per cent ($p < 0.30$) of control values, apparently owing to a compensatory response in some dogs. In each of the 3 subgroups of Group II, slight depression in the hematocrit was seen. These changes, however, were not statistically significant and may have been related in part to blood loss from the operative procedure.

Results were not tabulated for Group III because all of the animals receiving 1.05 ml. per kilogram of 70 per cent Urokon sodium died within 24 hours; consequently, follow-up renal function studies for determination of residual renal injury were impossible. Acute renal clearance studies were performed in some of these animals as in Group I, and severe immediate reduction in kidney function was present in all instances. The high mortality in this group of animals and the apparent severe reduction in renal function resulting immediately from the injection of this dose indicates the acute toxic effect on the kidney.

Clinical Observations.—In Table III are tabulated the immediate effects of aortography on renal hemodynamics and water and electrolyte excretion in man. No significant change in the general blood pressure response was seen. With the induction of anesthesia, glomerular filtration rate and renal blood flow both

fell to 82 per cent of control values. These changes were statistically significant ($p < 0.05$ and $p < 0.001$, respectively). Observations made following aortography were compared statistically with those made following induction of anesthesia as well as with control observations made prior to anesthetization.

Immediately following injection of 70 per cent Urokon sodium into the suprarenal portion of the abdominal aorta, glomerular filtration rate decreased from 82 to 59 per cent ($p < 0.01$) of control value prior to anesthetization. This represents a reduction of 28 per cent (75 to 54 c.c. per minute) from the postanesthesia value, a statistically significant depression ($p < 0.05$). Renal blood flow was depressed to an even greater degree than was glomerular filtration rate, that is, a reduction to 45 per cent ($p < 0.01$) of the value prior to injection of Urokon but following induction of anesthesia. One hour following injection of Urokon renal function had begun to return toward normal. Two hours following aortography, glomerular filtration rate had risen to 87 per cent of control values, an insignificant depression ($p < 0.30$). Renal blood flow, however, had returned to only 66 per cent of the preanesthesia control values ($p < 0.05$) or 80 per cent of the postanesthesia control values ($p < 0.20$). Thus, the depressions in glomerular filtration rate and renal blood flow 2 hours following aortography were not statistically significant ($p < 0.20$) if the values following anesthetization but prior to injection of Urokon are used for comparison.

Although urine volume fell to 57 per cent of control values following induction of anesthesia, little further change occurred following aortography. Urinary excretion of sodium and potassium fell to 55 and 89 per cent of control values, respectively, following anesthetization. Both returned to and exceeded control values ($p < 0.05$) following aortography, and urinary potassium excretion increased to 158 per cent ($p < 0.01$) of control values immediately following injection.

No significant changes in hematocrit or serum sodium were seen (Tables III and IV). Serum potassium fell slightly from an average value of 4.4 mEq. per liter during the control period to 3.8 mEq. per liter 2 hours following aortography ($p < 0.05$).

Twenty-four to forty-eight hours following aortography in man there were no statistically significant alterations of glomerular filtration rate (subgroup IIA $p > 0.50$ and subgroup IIB $p < 0.20$) or renal blood flow ($p < 0.30$) for either subgroup IIA or IIB. However, individually significant depressions were observed.

In Table V are tabulated the number of patients showing a residual depression (after 24 to 48 hours) in glomerular filtration rate of greater than 20 per cent of control values, divided into groups depending upon the amount of 70 per cent Urokon sodium injected. A depression in glomerular filtration rate of more than 20 per cent was not seen in any of the patients receiving 25 to 30 c.c. of contrast material, while it was present in 4 of 12 patients receiving 35 to 50 c.c. Alterations in renal blood flow are of less value than changes in glomerular filtration rate as evidence of renal damage because of daily variations in renal blood flow that are observed normally.

TABLE V. INFLUENCE OF DOSAGE OF 70 PER CENT UROKON SODIUM AS USED IN AORTOGRAPHY ON RENAL HEMODYNAMICS IN MAN

DOSE UROKON	NUMBER OF PATIENTS	NUMBER SHOWING NO RENAL DAMAGE	RENAL DAMAGE*	
			NUMBER	PER CENT
25 to 30 ml.	9	9	0	0
35 to 50 ml.	12	8	4	33.3
Total	21	17	4	14.3

*Renal damage as manifested by reduction in glomerular filtration rate of greater than 20 per cent.

The number of patients showing depression in glomerular filtration rate of more than 20 per cent following aortography, divided into groups according to the state of the aorta at the time of aortography, is recorded in Table VI. In 7 patients the aorta was normal or a properly functioning prosthesis was in place, and in 7 more the abdominal aorta was partially occluded below the renal arteries. Of these 14 patients, 6 received 25 to 30 ml. of 70 per cent Urokon sodium and the remainder received 35 to 50 ml. Patients with complete occlusion of the aorta received the larger dose in 4 instances and the small dose was given to 3. Although renal damage occurred in none of the patients with a completely occluded aorta 24 to 48 hours following aortography, this occurred in 4 (29 per cent) of those patients with partial or no occlusion of the aorta.

TABLE VI. INFLUENCE OF OCCLUSIVE DISEASE OF THE AORTA AT THE TIME OF AORTOGRAPHY ON RENAL HEMODYNAMICS IN MAN

STATE OF AORTA	NUMBER OF PATIENTS STUDIED	NUMBER PATIENTS RECEIVING 25 TO 30 ML. 70% UROKON SODIUM	NUMBER PATIENTS RECEIVING 35 TO 50 C.C. 70% UROKON SODIUM	NUMBER PATIENTS SHOWING NO RENAL DAMAGE	PATIENTS SHOWING RENAL DAMAGE*	
					NUMBER	PER CENT
Normal	7	4	3	5	2	28.6
Partially occluded	7	2	5	5	2	28.6
Total	14	6	8	10	4	28.6
Completely occluded	7	3	4	7	0	0

*Renal damage as manifested by reduction in glomerular filtration rate of greater than 20 per cent.

DISCUSSION

Both clinical and laboratory observations indicate that the immediate renal hemodynamic response to Urokon is vasoconstriction. This is manifested by depression of both the glomerular filtration rate and the renal blood flow. In the dog this was only slightly more pronounced if the aorta was occluded below the renal arteries during injection of the Urokon. In the human subject, chronic occlusion below the renal arteries due to arteriosclerotic occlusive disease does not appear to predispose the patient to renal damage following the intra-aortic injection of Urokon. The acute renal hemodynamic response then is functional confirmation of both experimental and clinical observations that the intra-arterial injection of contrast media is followed by vasospasm of the injected vessel and its tributaries.[2, 4, 5, 7, 11] Some persistence of this response

could be seen in both man and animal as long as 2 hours following aortography. Return to normal occurred in most instances after several days unless the amount injected was large enough to produce anatomic and functional damage to the kidney. This damage invariably resulted when the contrast medium was injected directly into the renal arteries. Under these circumstances the entire dose reached the renal parenchyma, since dilution and by-pass through collateral arterial channels were not possible. On the contrary, when the Urokon was injected into the aorta, even in the presence of complete occlusion of the aorta below the kidneys, the collateral circulation was adequate to prevent a seriously toxic dose from reaching the kidney.

The rapidity with which the acute renal hemodynamic response returned to normal appeared to be related primarily to the amount of contrast material reaching the kidneys. Although none of the patients receiving 25 to 30 ml. of 70 per cent Urokon sodium showed as much as 20 per cent reduction in glomerular filtration rate at the time of follow-up observations, 4 of 12 of the patients receiving 35 to 50 ml. showed a greater than 20 per cent reduction at that time. The course of 2 of these patients is shown in Table VII.

TABLE VII. THE COURSE OF RENAL DAMAGE FOLLOWING AORTOGRAPHY

PATIENT	AGE	MEAN BLOOD PRESSURE (MM. HG)				GLOMERULAR FILTRATION RATE (ML./MIN.)				RENAL BLOOD FLOW (ML./MIN.)			
		C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
B. J.	57	97	85	100		70	26	43	76	896	134	932	884
M. B.	67	84	67	75		61	36	21	85	896	661	505	794

C = Control observations, average of 3- to 10-minute periods.
D_1 = Observations immediately following aortography, average of 2- to 10-minute periods.
D_2 = Observations 24 to 48 hours following aortography, average of 3- to 10-minute periods.
D_3 = Observations 7 to 10 days following aortography, average of 3- to 10-minute periods.

Although occlusion of the aorta below the renal arteries during Urokon injection in the dog appeared to produce a slightly more pronounced depression of renal function in the period immediately following injection, after 3 to 5 days there was little difference between this group and the one in which the Urokon had been injected into the unoccluded aorta. Likewise in man it would appear that arteriosclerotic occlusion of the aorta below the renal arteries added no additional hazard to aortography. This observation is quite plausible when one refers to the preinjection control values in Table IV. In the presence of aortic occlusive disease (occlusion below renal arteries) renal blood flow is not increased but is actually less than that observed in individuals with normal aortas. Therefore, there would probably be no greater delivery of Urokon to the kidney after intraaortic injection in the patient with distal aortic occlusive disease than there would be in the patient whose aorta was not occluded. This is probably related to the development of collateral circulation.

The greatest depression of renal function seen in the experimental observations occurred in the cases in which the contrast material was injected into the left renal artery. When this was done, there was some immediate depression of

function on the uninjected side either owing to recirculation of Urokon to the contralateral kidney or as sympathetic renal hemodynamic response. However, by the end of 3 to 5 days, when renal function remained greatly depressed on the injected side, there was an actual general increase above control levels on the uninjected side.

In only one instance did we have the opportunity to study the effect of injection of the renal artery in a human. The details of this case are reported elsewhere.[1] Fifteen milliliters of 70 per cent Urokon sodium was injected with the tip of the needle in juxtaposition to the orifice of the right renal artery. The right renal artery and right kidney were brilliantly outlined in the roentgenogram taken at the completion of the injection, although enough contrast material went into the aorta to give a satisfactory aortogram, showing partial occlusion of both common iliac arteries. Unfortunately, control observations on glomerular filtration rate and renal blood flow were not obtained on this patient. However, 48 hours following aortography ureteral catheters were inserted and observations consisting of three 10-minute collection periods were obtained from each catheter simultaneously. These revealed that on the left, or uninjected side, glomerular filtration rate and renal blood flow were 60 and 570 ml. per minute, respectively, whereas on the right, or injected side, no measurable renal function was present.

These experimental observations tend to confirm the impression that renal damage results from excessive dosage of contrast medium. Excessively large doses of organic iodides or small amounts of inorganic iodides were given in all recorded instances of bilateral renal damage. Unilateral renal injury resulted from direct renal artery injection, and injury of this type occurred with the use of both large and small amounts of contrast medium. It is considered highly significant that renal damage did not occur in the 200 patients in our clinical series who received 25 c.c. or less of 70 per cent Urokon unless the renal artery was directly injected. On the other hand, early in our experience when proper dosage was not appreciated, 7 of the 100 patients who received more than 30 c.c. of 70 per cent Urokon developed renal damage from which 2 patients did not recover. Consequent to these observations, it would appear reasonable not to expect renal complications when doses of Urokon less than 35 c.c. are employed and direct renal artery injection is avoided.

SUMMARY

Although aortography is commonly considered an innocuous procedure, complications, predominantly renal, are being reported with increasing frequency. Studies were conducted on animals and on patients in an effort to elucidate those factors related to the development of functional renal changes following this procedure. Also, the pattern of functional alteration and degree of renal damage were quantitatively studied, determinations of glomerular filtration rate, renal blood flow, and water and electrolyte excretion being employed. Three variables with respect to the administration of Urokon were investigated: (1) dosage used, (2) site of injection, and (3) alteration in hemodynamics in the region of the kidneys.

The immediate hemodynamic response of the kidney to intra-aortic injection of Urokon appears to be vasospasm with depression of renal function. Although depression of function persists for some time when larger doses of contrast media are used in man, 25 to 30 ml. of Urokon sodium appears to be well tolerated. Accuracy in placement of the aortographic needle is of the utmost importance; injection of a renal artery produces severe damage to the kidney. Neither acute nor chronic occlusion of the aorta below the renal arteries appears to influence the production of renal damage following aortography.

Apparently because of inherent vasoregulatory mechanisms in the renal circulation, renal blood flow is not increased following aortic occlusion distal to the renal arteries. Therefore, there is no increase in Urokon delivered to the kidney following injection of this material when aortic occlusion is present. However, when Urokon is injected directly into the renal artery, the entire dose reaches the kidney since there is no collateral circulation to by-pass this organ.

These studies as well as clinical experience in 200 patients would appear to indicate that renal damage will not result from the use of 30 c.c. or less of 70 per cent Urokon if direct renal artery injection is avoided.

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A LONG-TERM STUDY OF EXTERNALLY SUPPORTED VENOUS AND ARTERIAL HETEROGRAFTS

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INTRODUCTION

CONSIDERABLE surgical effort has been devoted in recent years to the treatment of various diseases of the peripheral arterial system by resection or bypassing of diseased vessels. As interest in this field has increased, the problem of supplying satisfactory substitutes for the diseased arteries has grown proportionately. At present, an involved artery can be replaced either by another vessel or by an inert substance formed into a tube of the proper dimensions.

Although there has been increasing interest in the use of inert substances, many surgeons currently prefer to substitute a vessel for the diseased artery. In this regard autografts, homografts, and heterografts, either arterial or venous, have been used. In 1953 Hufnagel, Rabil, and Reed[3] reported the successful use of arterial heterografts, but the following year Creech and his associates[2] recorded less satisfactory results with this same type of graft.

The present study was undertaken to provide further observations on the results of heterografting, using both arterial and venous segments in the abdominal aorta. In an attempt to prevent aneurysmal dilatation of the grafts, they were wrapped in an inert plastic sponge of polyvinyl formal* after the vascular anastomoses were completed. Preliminary results of this study have been reported elsewhere.[5]

MATERIALS AND METHODS

In one experiment a segment of human saphenous vein, removed during a vein-stripping procedure, was used as the graft. All other grafts were obtained from young pigs which had been previously subjected to surface flash burns in another study. Segments of the aorta and inferior vena cava were removed under aseptic conditions when the pigs were sacrificed. The grafts were then placed in sterile Ringer's solution to which 1,000,000 units of aqueous penicillin had been added, and they were stored in an icebox at 3° C. until used. The period of storage varied from a few hours to 13 days, the majority of the grafts being used between 1 and 8 days after they were obtained.

Fifty-three adult mongrel dogs of both sexes, varying between 7 and 24 kilograms in weight, were used as subjects. In one instance an aortic graft was placed in the thoracic aorta under hypothermia. In all other experiments

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*Polyvinyl formal sponge supplied by O-Cel-O Division of General Mills, Inc., Buffalo, N. Y.

the graft was placed in the abdominal aorta between the renal arteries and the aortic trifurcation. Operations were performed using intravenous sodium pentobarbital anesthesia under aseptic conditions. The abdominal aorta was exposed through a midline or left rectus muscle-splitting incision, and a suitable segment of the vessel freed from the retroperitoneal tissues. After the aorta had been dissected out, it was clamped above and below with Potts aortic clamps and divided between the clamps. A short segment of the aorta was removed and a slightly longer graft substituted in its place. The grafts used varied between 1.5 and 4 cm. in length. The grafts, especially those of the venous type, were frequently somewhat greater in diameter than the recipient aorta. Everting mattress sutures of 5-0 arterial silk interrupted in two places were used to construct the vascular anastomoses. After removal of the Potts clamps and before abdominal closure, a rectangular piece of the polyvinyl formal sponge approximately 2 mm. in thickness was wrapped snugly around the graft and the adjacent aorta. The sponge was sutured to itself and not anchored to the aorta or retroperitoneal tissues. No anticoagulants or antibiotics were used during or after surgery.

Post-mortem examination of all animals dying after operation was carried out to ascertain the status of the graft. All animals which survived surgery were followed for periods up to 27 months before sacrifice. During this interval their clinical behavior was observed, the presence and intensity of femoral artery pulsations were noted and periodic percutaneous aortograms were done using 35 or 70 per cent solutions of Urokon sodium* as the contrast medium.

RESULTS

Of the 53 dogs subjected to surgery, 9 were rejected for analysis because of technical difficulties not bearing on the problem of heterografting. There remained for study 21 animals with venous and 23 with arterial grafts. Three of these animals, one with an arterial and 2 with venous grafts, had patent vessels at the conclusion of surgery, but complete graft thrombosis developed during the next 24 hours. At autopsy no error in technique was demonstrated, and these animals are, therefore, included in the study as acceptable subjects. The remaining 41 animals all had palpable femoral arterial pulsations for at least 24 hours after surgery. In analyzing the results it was found that failures could be divided into an early group occurring within the first 2 weeks and a late group occurring at some time after the second postoperative week.

Graft Failures.—Early graft failure occurred in 6 and later failure in 4 of the 21 animals with venous grafts, giving an over-all failure rate of 48 per cent. Three of the early failures were due to graft thrombosis. Graft rupture, almost complete graft dissolution, and combined thrombosis and rupture were found on one occasion each. The late difficulties were 2 instances of thrombosis, one of rupture in an aneurysmal graft 24 months after implantation, and one of graft replacement by a smooth cystic cavity.

Among the 23 animals with arterial grafts, 13 early failures and 2 late failures were seen. The resulting over-all failure rate was 65 per cent. Five

*Urokon sodium supplied by Mallinckrodt Chemical Works, St. Louis, Mo.

of the early failures were due to graft thrombosis and 5 to rupture. Almost complete dissolution was found in 2 instances. The final animal developed a false aneurysm with thrombosis, probably secondary to graft dissolution. One of the late failures occurred in a dog whose graft thrombosed over 17 months after surgery. The other late failure in the arterial graft series is a special case because the animal was the one with the graft placed in the descending thoracic aorta. This animal died suddenly 3 months after operation and was discovered at autopsy to have a large false aneurysm with secondary rupture and fatal hemorrhage into the pleural cavity.

Successful Grafts.—Five of the animals with successful vein grafts were followed less than 4 months before post-mortem examination. In 2 of these the grafts showed no sign of dilatation. The other 3 showed varying degrees of dilatation with one, the human saphenous vein graft, demonstrating a moderate fusiform aneurysm 4 months after implantation.

The remaining 6 animals with venous grafts were followed for 2 years before sacrifice. Periodic aortograms showed some alteration in graft contour in each instance. In 2 instances no further change occurred following the first aortogram 6 months after surgery, but distinct graft dilatation was present on the initial aortogram in these cases. Fig. 1 shows the specimen removed at autopsy in one of these dogs. In the remaining 4 animals definite progressive changes were noted in later aortograms. Fig. 2 shows the increase in graft dilatation between 12 and 18 months in one such case. Bizarre pockets and irregularities in graft contour were seen in several animals. Fig. 3 shows the internal appearance of one such graft. A polypoid mural thrombus is evident. In each animal followed for the 2-year interval the polyvinyl formal sponge was still in place, but it was greatly thinned and in places entirely absent. The presence of the sponge had not prevented dilatation of the graft in any instance although the formation of a true fusiform aneurysm was not common.

Of the 8 dogs with successful arterial grafts 2 were sacrificed about 2 months postoperatively. One of these animals was found to have a patent graft without dilatation. Through the entire graft about 40 per cent of its lumen along one wall was filled with an organized and endothelized thrombus. The second dog developed paraplegia directly after an aortogram which showed a patent vessel with distal irregular dilatation and a narrow distal suture line. Autopsy disclosed a fresh thrombus occluding the graft. There was also a rupture in the graft posteriorly with an old retroperitoneal hematoma occluding this defect. This graft might have failed later even without the added trauma of aortography.

There were 6 animals which were followed for 2 years or longer with functioning arterial grafts. In 3 of these little or no dilatation occurred during the follow-up period. Even in these vessels microscopic calcification was found in the wall of the graft and of the sponge. Dilatation in the remaining 3 grafts was not as marked as that seen in the venous group and true aneurysmal formation was not found in any case. Irregularities of graft wall and thinning or absence of the polyvinyl formal sponge were encountered just as they were

Fig. 1.—External appearance of a moderately dilated venous graft 2 years after implantation.

Fig. 2.—Aortograms of an animal with a venous graft 12 and 18 months after its implantation. Note definite increase in graft dilatation.

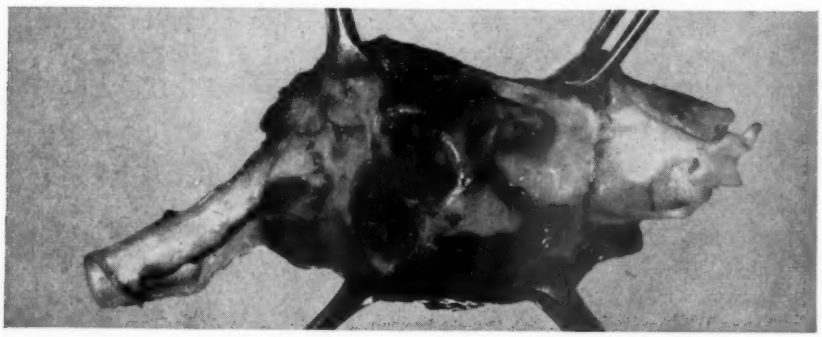

Fig. 3.—Internal appearance of a venous graft. Note polypoid mural thrombus and irregular wall 2 years after implantation.

with vein grafts. In other cases, however, the formed arterial wall of the graft had disappeared leaving only a smooth, translucent layer between the vessel lumen and the fibrous tissue in the interstices of the sponge.

A feature of almost all the grafts, either venous or arterial, followed for a period of months was definite constriction at the suture lines between host vessel and graft. The aortogram in Fig. 2 demonstrates this point. Suture line constriction occurred even when the aorta and the graft were tailored so that the vessel diameter at the anastomosis was slightly greater than the diameter of the host aorta or of the grafted segment. Constriction was not associated with the surrounding sponge which was deliberately placed to extend well beyond either end of the graft.

Microscopic studies of the grafts confirmed the findings of Carrel[1] and others[2, 7] that the heterograft becomes essentially a fibrous tube with medial elastic fibers inconspicuous or absent. In the first few months after surgery the elastic fibers were swollen and hyalinized with absent or pyknotic nuclei. Later these fibers were replaced by an acellular fibrous tissue with focal areas of calcification. The polyvinyl formal sponge showed a proliferation of fibrous tissue in its interstices with minimal foreign body reaction in sections taken at various times postoperatively.

DISCUSSION

The failure rate in our experience of 48 per cent for the venous and 65 per cent for the arterial grafts is a prohibitive one. This may be associated with the method of preservation employed. Kimoto and his colleagues[4] reported 3 successful heterografts of 8 attempted in dogs when grafts were stored in Ringer's solution with added serum. In contrast to this, 19 of 21 grafts were successful when storage was carried out in absolute or 70 per cent ethyl alcohol. They felt that denaturization of the graft protein by the alcohol was important in the increased rate of success with this method. In a similar study Rosenberg and his associates[6] reported that 70 per cent of their arterial heterografts were successful when controlled enzymatic digestion was used to remove the protein components of the graft.

We have not used grafts prepared by either of these methods in our studies. However, a preliminary experiment with freeze-dried heterografts was carried out. This study was abandoned because of considerable early difficulty with thrombosis or rupture.

Aneurysmal formation was a frequent finding in the venous grafts when they were followed for a long enough period after surgery. The supporting sponge did not prevent this dilatation, although fatal hemorrhage from early graft rupture may have been forestalled by the sponge in several instances. The arterial heterografts were less prone to dilatation, but the problems of thrombosis and rupture remained.

The finding of stricture at the suture lines was a common one with both types of heterograft. Hemografts and various prosthetic materials, used in this

laboratory in similar experiments, have not developed suture line stricture to this degree. It would appear that the problem of stricture is a unique one to the heterograft, at least under the conditions of the present experiment.

Graft success in experiments of this type must be evaluated in terms of actual visualization of the graft. Several of our animals which were clinically well and had strong femoral arterial pulsations were found at autopsy or by aortography to have graft thrombosis. Even in those grafts which were successful in terms of adequate function over a long period, inspection of the grafts at post-mortem examination did not appear encouraging. In these vessels the intimal surface was usually rough. Frequently membranes extended part way across the lumen, and organized mural thrombi projected into the vessel not uncommonly. Usually 3 or 4 mm. of the graft wall at either suture line appeared fairly normal, but the rest of the graft was variable and bizarre with the entire wall quite thin in comparison to the host aorta. The contrast between the appearance of these grafts and the smooth intimal surface of a successful Vinyon-N graft followed for a prolonged period is evident in Fig. 4.

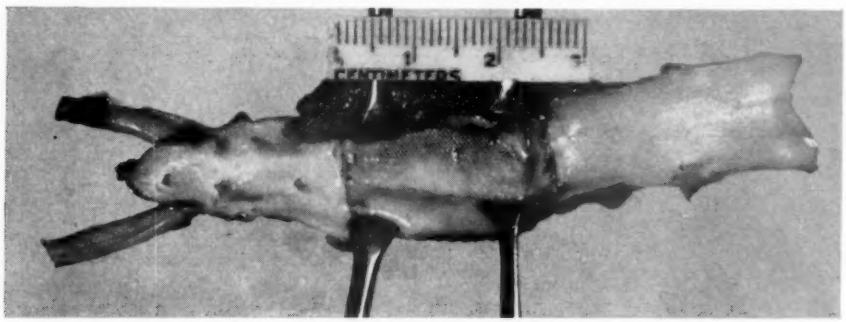

Fig. 4.—A Vinyon-N graft 2 years after implantation. Most of the heterografts were not this smooth internally.

These studies did not evaluate directly the possibility of host-graft incompatibility. However, the findings of early frank graft necrosis on several occasions, as well as the high incidence of early complications, suggest that such an incompatibility may be important. Graft necrosis of this type has not been encountered here in homograft work.

There are few long-term studies of heterografts reported in the literature. Our experience, and that of Wesolowski and Sauvage,[8] would indicate a conservative attitude toward heterografting until favorable long-term studies are recorded.

SUMMARY AND CONCLUSIONS

1. Venous and arterial heterografts from the pig were placed in the aorta of the dog and long-term follow-up studies undertaken. These grafts were externally supported by a polyvinyl formal sponge.

2. The early failure rate with both types of graft was high. This was especially true with the arterial group. The common complications at this stage were thrombosis and rupture.

3. As the follow-up period lengthened, aneurysmal dilatation occurred in the venous grafts despite the surrounding sponge.

4. Frank aneurysm did not occur with the arterial grafts, but the vessels showed bizarre thrombi, membranes, and roughened areas on their intimal surfaces.

5. Vascular heterografting, with the techniques reported in this experiment, is not a satisfactory procedure.

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THE USE OF ENDOTRACHEAL CUFFS TO CONTROL BLEEDING THROUGH SYNTHETIC ARTERIAL GRAFTS

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FROM a questionnaire sent to vascular surgeons by the Committee for the Study of Vascular Prostheses of the Society for Vascular Surgery,[1] it was learned that most of these surgeons felt that the property of permeability was an important attribute of a prosthetic graft. Their impression was that the growth of fibrous connective tissue through the interstices of the material affixed the prosthesis to the tissues and also accelerated organization of the fibrin deposit on the inner surface of the graft. In the report of this Committee it was stated that "the pervious prostheses bleed momentarily until clotting occurs in the interstices, and this may constitute a serious problem as indicated by the report of two deaths resulting from uncontrollable hemorrhage through the walls of the prostheses."

In general, our experience with the Edwards-Tapp* crimped nylon tube has been satisfactory. However, excessive bleeding through the graft directly after release of the occluding clamps has been a disturbing feature. On occasions, as much as 700 to 1,000 c.c. of blood has been lost within a few minutes. Since many of our patients are in the older age group and may have arteriosclerotic heart disease, this sudden loss of blood imposes an additional hardship to their myocardial function.

Preclotting the outside of the graft with 50 c.c. of the patient's blood has not proved helpful in preventing leakage through the graft. Manual pressure with the aid of laparotomy pads against the graft has not been effective since the pressure is expended in an anteroposterior direction only and the degree of pressure is difficult to ascertain and to control. In addition, improperly applied pressure might encourage thrombosis of the graft or dehiscence of the suture line. Because of these considerations, an endotracheal cuff was employed in the research laboratory as a method of applying even, nontraumatic, controlled, and circumferential pressure against the synthetic prosthesis. Inflation of the cuff to 120 to 140 mm. Hg, controlled by a manometer, abolished the loss of blood through the interstices of the graft which was used to bridge a defect in the dog's abdominal aorta. It did not, however, prevent the flow of blood into the distal artery. The cuff was long enough to cover the graft and both suture lines (Figs. 1 and 2). When the cuff was deflated at one minute and again at two minutes after release of the arterial clamps, bleeding ensued. Prior to deflation, the absence of bleeding was striking. Finally the

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cuff was left inflated for five minutes and then released. Bleeding was completely eliminated by this maneuver in four successive dogs. At this point the endotracheal cuff was divided with scissors and removed. Prior to its removal,

Fig. 1.

Fig. 2.

Fig. 1.—The endotracheal cuff is in place and the anastomoses have been completed.
Fig. 2.—The endotracheal balloon has been inflated just prior to removal of the occluding clamps.

the cuff can be reinflated after a minimal loss of blood if bleeding should take place after its release. Previously, more laparotomy pads had to be reapplied to the graft but only after the loss of a considerable amount of blood. Sanger[3]

stated that "Frequently it is necessary to reapply the clamp many times before seepage actually stops." Reclamping of the artery should be avoided because it would encourage thrombosis of the entire graft.

Presently we are attempting to modify the inflatable cuff designed by Jacobson and McAllister[2] so that it can be used in the human. In the meantime, a series of endotracheal cuffs will be used to surround the long grafts.

CONCLUSION

The use of an inflatable cuff around a synthetic graft eliminates bleeding through the graft wall in the dog. The principle of controlled, nontraumatic, and reproducible circumferential pressure seems to be sound. Its application to the human being will be forthcoming.

We are indebted to Mr. Edward Dubin for his technical help and suggestions.

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SIMULTANEOUS PULMONARY VALVULOTOMY AND RESECTION FOR PULMONARY TUBERCULOSIS

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THE simultaneous occurrence of a pulmonary valvular stenosis and pulmonary tuberculosis is rather common. The explanation may be the reduced blood flow through the lungs. A normal ventilation and reduced blood flow will cause a relatively lower oxygen uptake from the alveoli, resulting in a comparatively higher oxygen concentration in the lung tissue. This improves the condition for growth of the tubercle bacilli. The experimentally produced tuberculosis which was more pronounced on the side where an anastomosis between the subclavian and the pulmonary artery was created (Hanlon) supports this theory. Another indication is the work by Carlens and Mattson[3] with lobospirometry with the patients in erect and supine positions, explaining the high incidence of tuberculosis in the upper lobes.

In a series of 62 patients with untreated pulmonary stenosis the average length of life was 26 years and in 10 the cause of death was ascribed to tuberculosis (Greene and associates[4]).

In spite of the rather common occurrence of pulmonary tuberculosis and pulmonary valvular stenosis, only one case has been described earlier in which both conditions were treated simultaneously. Following a left pneumonectomy and pulmonary valvulotomy the pressure in the right ventricle decreased from 200/0 to 83/0 mm. Hg (Soutter and associates[6]).

CASE REPORTS

CASE 1.—In 1953 hemoptysis occurred in a 32-year-old man and a tuberculous infiltration in the left upper lobe was diagnosed. A year later a tuberculous cavity was seen in the left upper lobe and the sputum was positive on direct smear. A harsh systolic murmur was heard over the heart. Catheterization showed a pressure in the right ventricle of 170/10 mm. Hg. Cardioangiography was not performed. The oxygen uptake of the left lung was 45 per cent of the total. The maximal breathing capacity was 117 L. per minute.

The preoperative diagnosis was tuberculous cavitation in the left upper lobe and stenosis valvulae pulmonalis (Fig. 1).

At operation (March 16, 1954), a resection of the apicoposterior and anterior segments of the left upper lobe plus transarterial pulmonary valvulotomy and osteoplastic roof thoracoplasty were performed.

When the segmental resection had been completed, a Potts-Riker knife was introduced through the divided apical segmental artery down into the right ventricle. After the knife had been opened, it was very difficult to force it back into the pulmonary artery and considerable traction had to be applied to cut through what was believed to be the valvular dome. The incision was enlarged in the pulmonary artery and a Brock dilator was introduced into the right ventricle. At first it was difficult to draw the opened dilator back into the pulmonary artery, but after dilatation several times it could be passed easily through the pulmonary valves. The finger was not introduced into the right ventricle for control of the result by palpation.

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Fig. 1.—Case 1. X-ray showing tuberculous cavity in the left upper lobe.

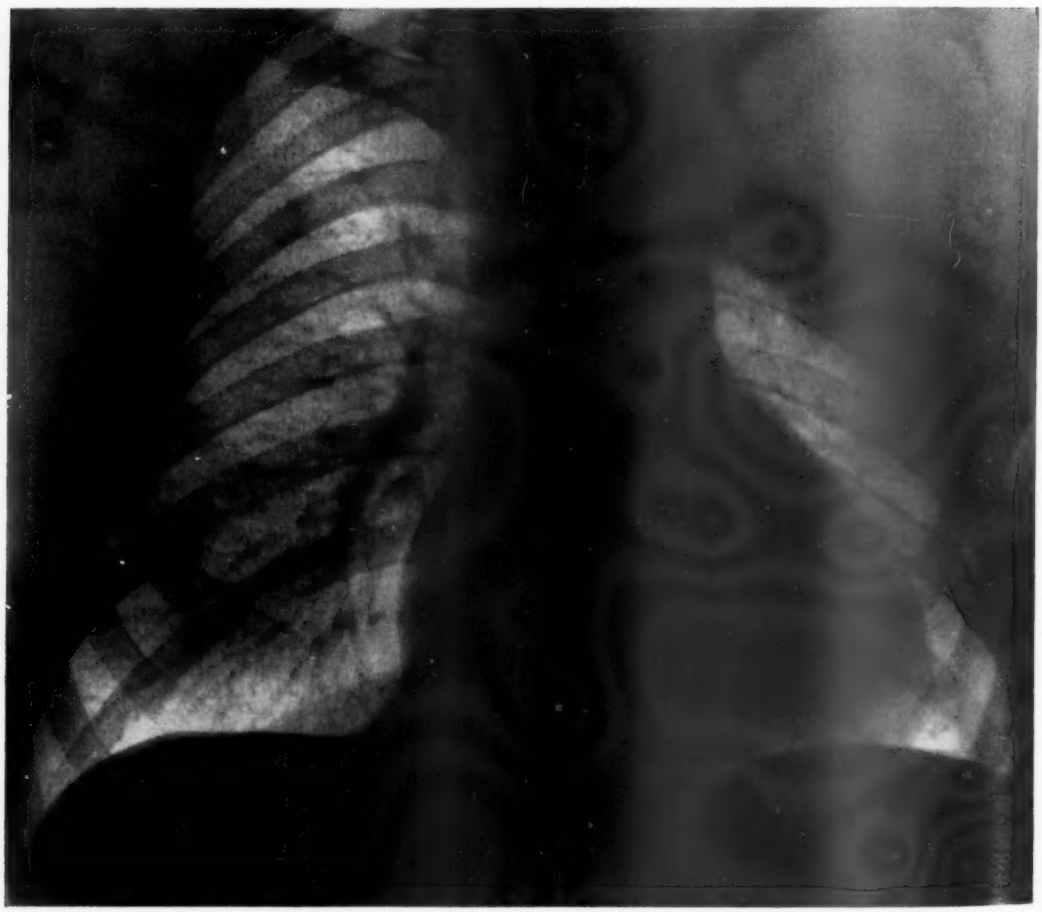

Fig. 2.—Case 1. X-ray of the chest 2½ years after resection of the apicoposterior and anterior segments of left upper lobe with osteoplastic thoracoplasty.

For a year after the operation the patient felt much better and could climb 4 stairs at a time. His general condition then deteriorated, with peripheral edema and shortness of breath on exercise. Two and one-half years after operation the oxygen uptake on the left side was 28 per cent of the total and the ventilation was 29 per cent of the total. Sputum and gastric washings were negative on culture and guinea pig test.

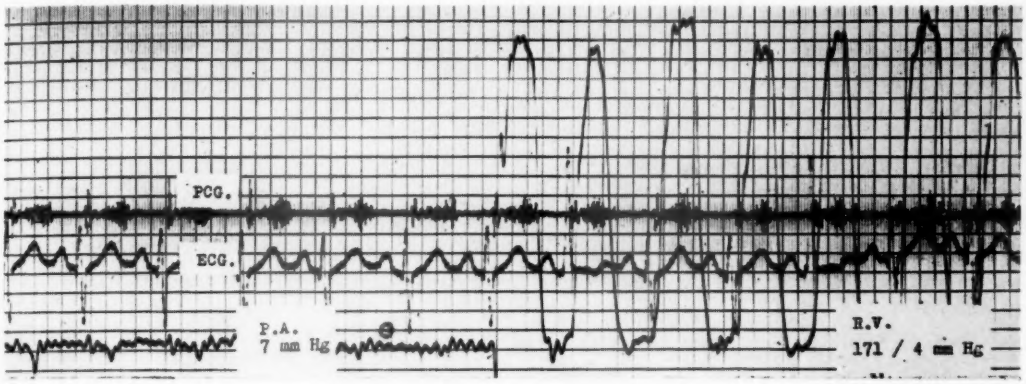

Fig. 3.—Case 2. Withdrawal pressure curve from the pulmonary artery (PA = 7 mm. Hg) to the right ventricle (RV = 171/4 mm. Hg).

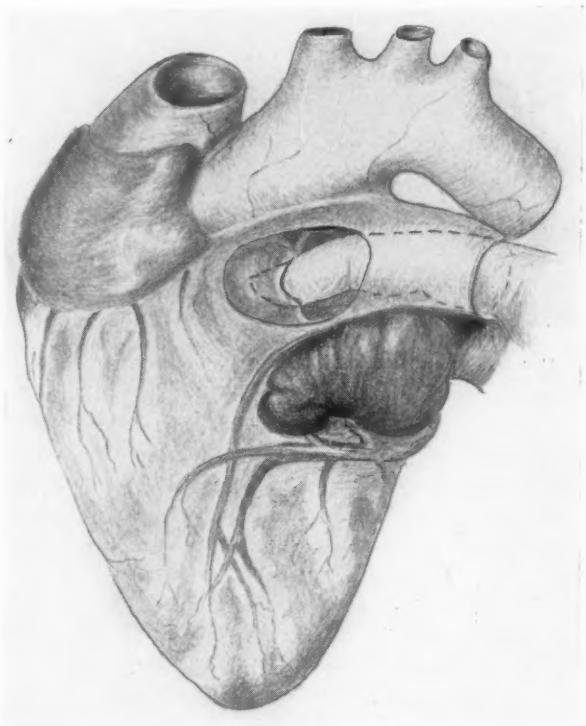

Fig. 4.—A finger is introduced through the left pulmonary artery to control the result of valvulotomy.

The right ventricular pressure, however, was still 167/3 and cardioangiography showed an infundibular stenosis. After the left osteoplastic thoracoplasty it was considered impossible to perform a bilateral thoracotomy for open cardiotomy and infundibular resection under direct vision with the help of a heart-lung machine (Fig. 2). The heart was rotated to the left and the infundibular stenosis was deemed inaccessible from the right chest.

At the second operation (March 13, 1957), therefore, a longitudinal sternum-splitting incision was made. Due to rotation of the heart and the earlier operation the base of the pulmonary artery was dislocated far to the left. It was necessary, therefore, to free the pericardium from the left lung down to the left pulmonary veins in order to rotate the right ventricle forward by traction in the pericardium. A closed infundibular resection according to Brock[2] was performed, resulting in a systolic pressure drop from 120 to 80 mm. Hg in the right ventricle and a systolic pressure increase from 20 to 30 mm. Hg in the pulmonary artery. The postoperative course was uneventful.

CASE 2.—A 36-year-old woman with congenital heart disease had had dyspnea and cyanosis since childhood. For the last 10 years she had had edema of the legs in the evenings. In 1944 she developed hemoptysis, and x-ray investigation demonstrated a tuberculous cavity in the left upper lobe. She had received treatment in a sanatorium for almost 10 years. In 1953 a three rib thoracoplasty was performed on the left side but was complicated by paralysis of the diaphragm. Angiocardiography showed an isolated pulmonary valvular stenosis. Heart catheterization showed a high pressure in the right ventricle (171/4 mm. Hg) and a slight right-to-left shunt on the atrial level (Fig. 3). The maximal breathing capacity was 64 L. per minute.

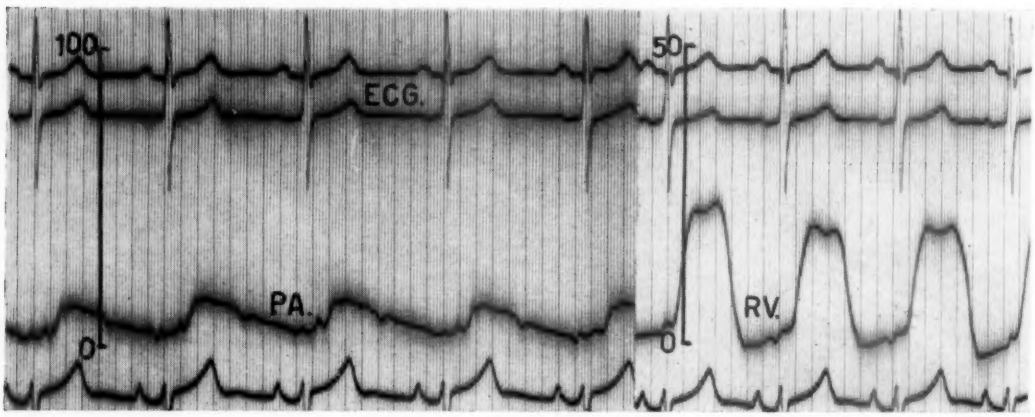

Fig. 5.—Case 2. Pressure curves one year after operation with pneumonectomy and pulmonary valvulotomy. The pressure in the pulmonary artery was 17/6 mm. Hg (mean pressure = 12 mm. Hg) and in the right ventricle 24/3 mm. Hg.

The diagnosis was tuberculous cavitation in the left upper lobe plus isolated pulmonary valvular stenosis. At operation Dec. 8, 1954, a resection of the left upper lobe plus a wedge from the apex of the left lower lobe and a transarterial pulmonary valvulotomy were performed. After the valvular dome had been cut and dilated, a finger was introduced through the pulmonary artery to control the result (Fig. 4). The operation was complicated by an infected hematothorax followed by a bronchopleural fistula. On Jan. 21, 1955, an extrapleural resection of the remaining part of the left lung and of the remaining ribs including the ninth rib was performed. The bronchus was closed at the level of the carina.

The postoperative course was uneventful. A year later the pulmonary artery pressure had decreased from 171/4 to 17/6 mm. Hg (Fig. 5). Culture and guinea pig test on sputum were negative. The maximal breathing capacity was 46 L. per minute. The patient did not complain of shortness of breath and could climb 3 stairs at a time.

DISCUSSION

The first case illustrates most of the diagnostic and therapeutic errors that can be made.

Three years ago we did not know that an infundibular stenosis with an intact ventricular septum is a rather common congenital malformation which is encountered in 20 per cent of all cases of pulmonary stenosis. As we believed at that time that practically all cases with intact septum and pulmonary stenosis were valvular, we did not confirm the diagnosis by angiocardiography but relied upon pressure measurements alone. If there is a small third ventricle it may be difficult to obtain its pressure on the withdrawal curve. Cardioangiography is therefore indicated.

The second fault was not to control the result obtained by palpation after introduction of a finger through the pulmonary artery. As we have seen a case earlier with infundibular stenosis returning to normal right ventricular pressure after a closed infundibular resection according to Brock, we chose this technique as being the only possible operation in a case with left osteoplastic roof thoracoplasty.

In the surgery of pulmonary valvular stenosis we have encountered two different pathologic conditions.

1. In one case where valvulotomy was performed under direct vision during inflow occlusion and perfusion of oxygenated blood into the aorta, the pulmonary valves were fused together into a flaccid rather thin membrane with a central opening. When viewed from the pulmonary artery, 3 raphes could be seen extending from the central perforation over the superior surface of the dome-shaped membrane to the wall of the pulmonary trunk. In this type nothing is gained by a precise incision in the raphes. The same functional result will be obtained if the membrane is divided out to the arterial wall by two opposite incisions. As there were no real commissures, nothing more could be achieved than a division of a diaphragm. The elasticity of the dome caused an operative problem. The original instruments used sometimes only stretched the hole so that only a slight reduction of the pressure gradient was obtained at the follow-up examination.

2. In the other type of isolated pulmonary stenosis, the pulmonary valve is represented by a conical fibrous funnel. Then the radiating raphes representing the fused commissures are easily seen. Case 2 was of this type. The difficulty encountered was the firmness of this fibrous funnel. Only after cutting with the sharp Potts-Riker knife and dilation with dilators and with the finger introduced through the pulmonary artery an effective opening could be obtained and right ventricular pressure be brought to normal.

In the treatment of pulmonary valvular stenosis it is essential first to use a sharp instrument, either a knife or scissors, and then adequate dilators. In our clinic Crafoord introduced his finger through the right ventricular wall to confirm the result obtained by the Brock procedure. In Case 2, in which simultaneous resection of the left lung was performed, it was easy to make a longitudinal incision in the left pulmonary artery for instrumentation and digital control. After cutting with a knife a rather forceful dilation of the fibrotic funnel had to be made by the finger.

Recently Søndergaard[5] designed scissors for valvulotomy through the pulmonary artery. The scissors are introduced through Søndergaard's ring clamps.

Since normal right ventricular pressures were obtained, we were satisfied with the procedure. If resection from the right lung had been necessary at the same time, we would have performed the valvulotomy through the right ventricle. One patient with isolated pulmonary valvular stenosis died 3 days after a Brock procedure with valvulotomy through the right ventricle. At autopsy it was evident that the result would have been the same if an open operation had been performed.

This finding, together with the follow-up with normalized pressures after the procedure described, has persuaded us at present to agree with Varco[7] who, after a considerable experience, now believes that the open operation offers nothing special in the correction of pulmonary valvular stenosis. Recently we operated upon a child of 10 months with isolated pulmonary valvular stenosis. This child had too small a pulmonary artery for a closed operation. Through a sternum-splitting incision and with inflow occlusion, the pulmonary artery was opened and the commissures cut with scissors. This operation was originally described by Varco and was found to be so easy to perform without hypothermia that we have used it in 2 other patients.

SUMMARY

In two cases left-sided pulmonary cavitary tuberculosis and pulmonary stenosis were simultaneously treated. When resection was completed the left pulmonary artery was used for instrumentation and digital control of the valvulotomy. The right ventricular pressure decreased from 170/10 to 17/6 mm. Hg in Case 2. In Case 1 an infundibular stenosis was present but not diagnosed at the first operation. As this patient did not improve an infundibular resection according to Brock had to be performed at a second operation.

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STUDIES OF LIVER FUNCTION DURING EXTRACORPOREAL CIRCULATION WITH LOW FLOW RATE

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UNTIL recently a major portion of the work with artificial pump-oxygenators has been directed toward developing a machine which could be used with a high survival rate. Now that such machines are in successful use more detailed investigations of the physiologic effects of extracorporeal circulation are being carried out. Such information is essential to increase the safety of this technique for the relatively short periods necessary for most intracardiac operations and also to make possible extension of its use for longer times and other conditions.

Interest in the effect on the functional status of the liver was stimulated by certain clinical observations in patients undergoing open heart operations.[5] It was noted that a high percentage of such patients complained of unusual crampy abdominal pain in the early postoperative period without evident cause, and Bromsulphalein extraction studies in certain patients indicated a degree of impairment of liver function after operation. One patient, who had undiagnosed cirrhosis, died of liver failure 4 days postoperatively. In addition a metabolic acidosis with elevation of lactic acid has frequently been observed[1, 2] and derangement of hepatic metabolic activity was suspected as a contributory cause.

During the past several years a pump-oxygenator has been developed in this institution which has been successfully used in experimental animals and in patients.[5, 13] As part of a continuing plan of investigation of the effects of extracorporeal circulation on the body physiology, an experimental study of the status of the liver during and immediately after heart-lung by-pass was carried out. In order to approximate conditions commonly obtained in operations on humans, perfusion flow rates were deliberately maintained at rather low levels.

METHODS

The pump-oxygenator used in these experiments is the Crafoord-Senning type delivering a flow of low pulsation at 280 beats per minute. The oxygenator consists of multiple perforated rotating cylinders which expose a thin film of blood to an oxygen atmosphere. The apparatus is so designed that the pump

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output is automatically balanced with venous return, accounting for the moderate variation in flow rate observed during by-pass. Fresh heparinized donor blood was used to fill the machine.

A double-lumen cannula was devised which provided isolated hepatic venous drainage for blood sampling and measurement of hepatic blood flow and also served as a collection cannula to lead venous blood to the pump-oxygenator (Fig. 1). Hepatic blood samples were aspirated through a needle inserted into the cannula. By temporarily occluding the tube, hepatic venous blood could be

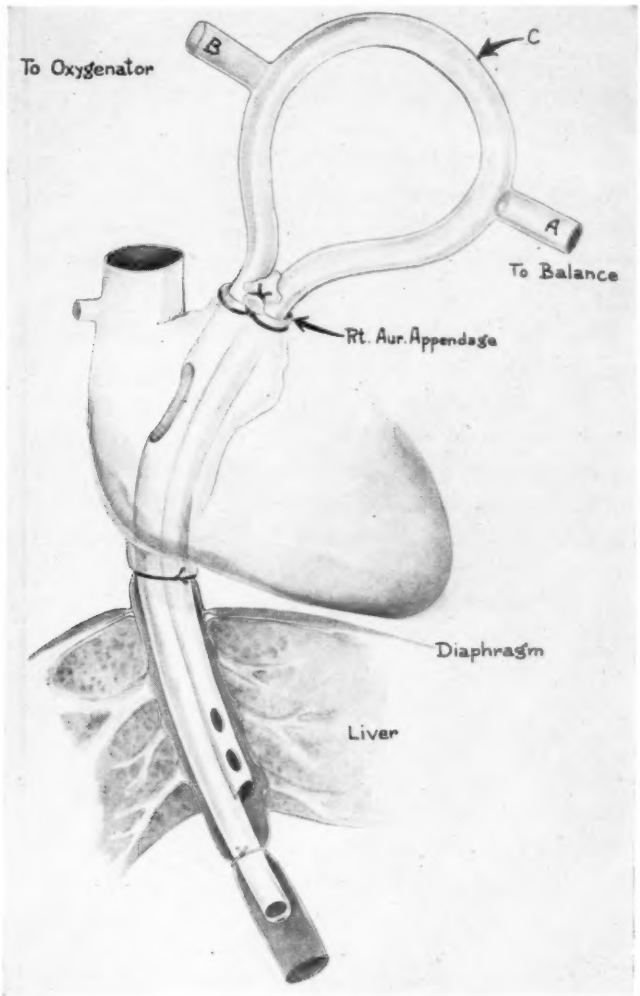

Fig. 1.—Cannula for isolation of hepatic venous flow. The cannula is passed through the right auricle and down the inferior vena cava. When the ligatures above and below the liver are tightened all hepatic venous blood flow is diverted into the shorter tube of the cannula, then passes through the exterior tube (outlets *A* and *B* being occluded) and escapes into the right auricle through the same outlet as inferior vena caval blood.

Simultaneously occluding the tube at *C* and opening outlet *A* diverts all hepatic flow through this side arm for measuring hepatic blood flow. The level of the collecting bag was adjusted to the level of the right auricle and atrial pressure.

When outlet *B* is opened, superior vena caval blood enters the tube through the opening lying in the right auricle, and together with inferior vena caval and hepatic venous blood is led to the pump-oxygenator through side arm *B* (the pulmonary artery is occluded simultaneously).

diverted through a proximal side arm into a thin-walled, low-resistance collecting bag lying on a balance pan. By allowing a predetermined weight of blood (50 Gm.) to flow into this bag and noting the elapsed time, hepatic blood flow could be calculated and the blood readily returned to the circuit.

Pressures were measured with Elema strain gauges and recorded on a Speedomax potentiometer.

Lactic acid was determined by the method of Pfleiderer and Dose.[12]

Potassium was measured with a flame photometer.

Bromsulphalein levels were measured by direct photometry before and after alkalinization.

OPERATIVE PROCEDURE

Mongrel dogs were anesthetized with intraperitoneal Nembutal, 30 to 35 mg. per kilogram, and maintained on positive-negative artificial ventilation throughout the experiments except during the period of heart-lung by-pass. Heparin, 4 mg. per Kilogram, was given intravenously prior to cannulization.

Catheters were passed into the abdominal aorta and inferior vena cava through the femoral vessels to be used for blood sampling and pressure measurement.

Through a short right subcostal incision a plastic catheter was passed into the portal vein through a branch for pressure recording and blood sampling. A sling ligature was passed around the inferior vena cava just below the liver and later tightened about the longer tube of the double-lumen cannula.

Through a right thoracotomy the double-lumen cannula was passed through the right auricular appendage into the inferior vena cava. This maneuver was facilitated by first bringing the previously placed femoral-caval cannula out through the appendage and threading it through the longer tube of the double-lumen cannula to be used as a guide. A sling ligature was passed around the vena cava just above the diaphragm and tightened around the cannula, diverting all hepatic venous outflow into the shorter tube. A cannula was placed into the aorta through the left subclavian artery and connected to the pump for extracorporeal circulation.

During heart-lung by-pass, which was carried out for 60 minutes in each experiment, the pulmonary artery was occluded by a sling ligature.

In each case after placement of all cannulae the dog seemed to be in good condition; mean arterial blood pressure ranged from 75 to 110 mm. Hg.

The following studies were then carried out before, during and after heart-lung by-pass.

1. Pressures were recorded continuously in the aorta, inferior vena cava, and portal vein, and hepatic blood flow and extracorporeal flow rate were noted intermittently.

2. Lactic acid concentration was measured in blood from portal vein, hepatic veins, aorta, and inferior vena cava.

3. Potassium concentration was measured in blood from the portal vein and the hepatic veins.

4. Bromsulphalein extraction was determined by giving single injections of BSP intravenously and measuring the concentration in blood from the portal vein and hepatic veins every 5 minutes for 20 minutes after injection.

Operations were performed with clean but not sterile technique and all dogs subsequently killed. In each case the condition of the animal was good after perfusion with pulse and blood pressure approximating control levels.

Control experiments were carried out using the same technique of operation and cannulization, and observations were made over similar time intervals but without the period of extracorporeal circulation. These were principally of value in analysis of the effects of extracorporeal circulation on BSP extraction as discussed below.

RESULTS

Pressure Response.—In 7 dogs simultaneous recordings were made of pressure in the aorta, inferior vena cava, and portal vein. A typical record is illustrated in Fig. 2; similar patterns of response were noted in all dogs, varying only in degree.

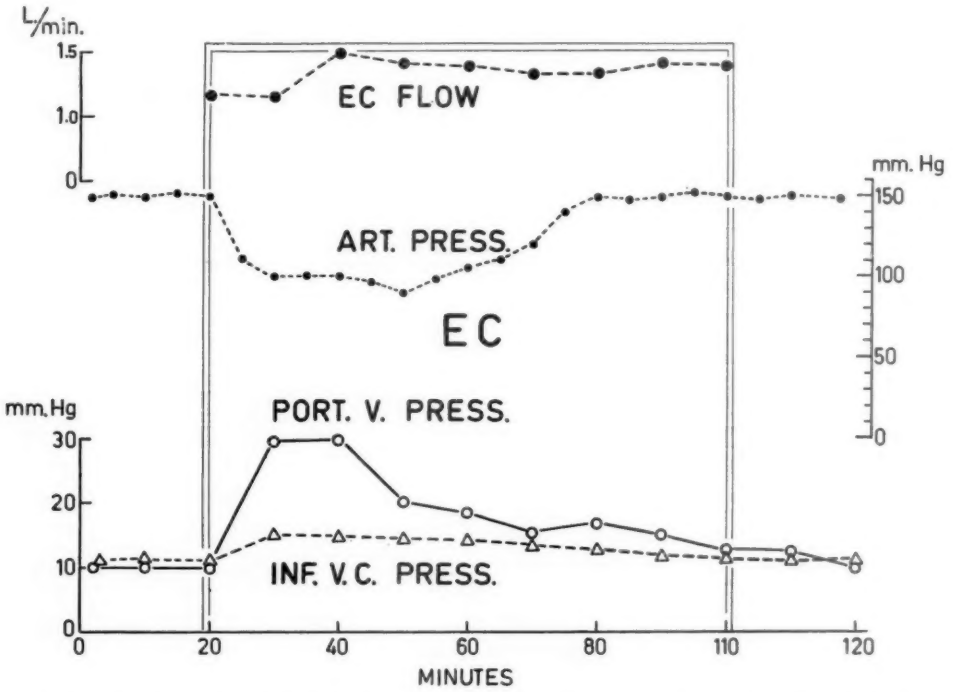

Fig. 2.—A typical experiment illustrating pressure and flow relations. "EC" indicates the period of extracorporeal circulation. (18 Kg. dog.)

Immediately after beginning extracorporeal circulation, arterial pressure fell sharply, the decrease depending upon the extracorporeal circulation flow rate. Following this early decrease, the pressure usually rose moderately, occasionally reaching the control level at higher rates of flow.

Pressure in the inferior vena cava evidenced a prompt rise from an average of 8.7 to 16.0 mm. Hg (84 per cent increase). The pressure rose to maximum

levels in the first 3 or 4 minutes of extracorporeal circulation and then decreased steadily, usually returning to approximately control levels in 10 to 12 minutes.

Portal vein pressures showed a more marked elevation, rising from an average level of 9.5 to 24.5 mm. Hg (136 per cent increase). This increase in pressure was not only appreciably higher than that occurring in the vena cava but was also maintained for a longer period, usually returning to near normal levels in approximately 20 minutes.

Extracorporeal Flow Rate and Hepatic Flow.—Perfusion flow and change in hepatic blood flow in another group of 5 dogs are given in Table I. In one experiment the flow ranged from 29 to 45 ml. per Kilogram per minute, in one from 36 to 43 ml. per Kilogram per minute, and in the remainder the flow was maintained at 51 to 63 ml. per Kilogram per minute.

TABLE I

EXPERIMENT	EXTRACORPOREAL CIRCULATION FLOW (ML./KG./MIN.)	HEPATIC FLOW (PER CENT CHANGE)*
113	52 – 63	± 0
107	53	– 8
612	51 – 55	– 15
131	36 – 43	– 18
141	29 – 45	– 14

*Flow during EC compared to control period.

In the experiment during which the highest flow rate was maintained there was no decrease in hepatic blood flow. In the remaining experiments hepatic blood flow decreased 8 to 18 per cent during by-pass with no consistent correlation of decreasing hepatic blood flow to extracorporeal circulation flow rate.

Actual hepatic flow rates during control periods averaged 18 ml. per Kilogram per minute, a lower figure than is usually obtained by indirect methods of estimation of hepatic blood flow.[3] This may be accounted for in part by the trauma of surgery.

Lactic Acid.—Lactic acid metabolism by the liver was estimated by determining the relative concentrations in blood entering and leaving the liver.

Samples taken simultaneously in portal vein and aorta (to indicate hepatic artery levels) showed essentially the same lactic acid concentrations with an average difference of only 0.10 mEq. per liter, and since the major portion of hepatic blood flow is provided by the portal vein this source was used to indicate lactic acid levels in blood entering the liver.

Fig. 3 illustrates the comparative values for lactic acid in blood entering and leaving the liver before, during, and after the period of heart-lung by-pass. In general the rate of withdrawal of lactic acid by the liver was maintained at control levels. In the one dog in which the liver failed to withdraw lactic acid the same situation occurred during the control period.

During extracorporeal circulation systemic concentration of lactic acid rose an average of 22 per cent, a phenomenon also noted in humans.[5, 6] A consistent elevation of lactic acid was found in inferior vena caval blood suggesting an increased production peripherally.

Potassium.—There was a general tendency for systemic levels of potassium to decrease slightly but no consistent or significant changes were observed in hepatic vein concentrations which would indicate unusual liberation of potassium by the liver during extracorporeal circulation.

Bromsulphalein.—Measurement of the chromoexcretory function of the liver by either the older retention test or the calculated plasma clearance rate did not seem satisfactory for the conditions of these experiments. Half-life is affected by the changes in plasma volume resulting from the addition of blood in the pump-oxygenator to the circulation, and calculation of plasma clearance rate depends upon an accurate measurement of plasma volume which was not obtained in these experiments (the usual technique using Bromsulphalein concentration to determine plasma volume was not considered sufficiently precise to give valid results).

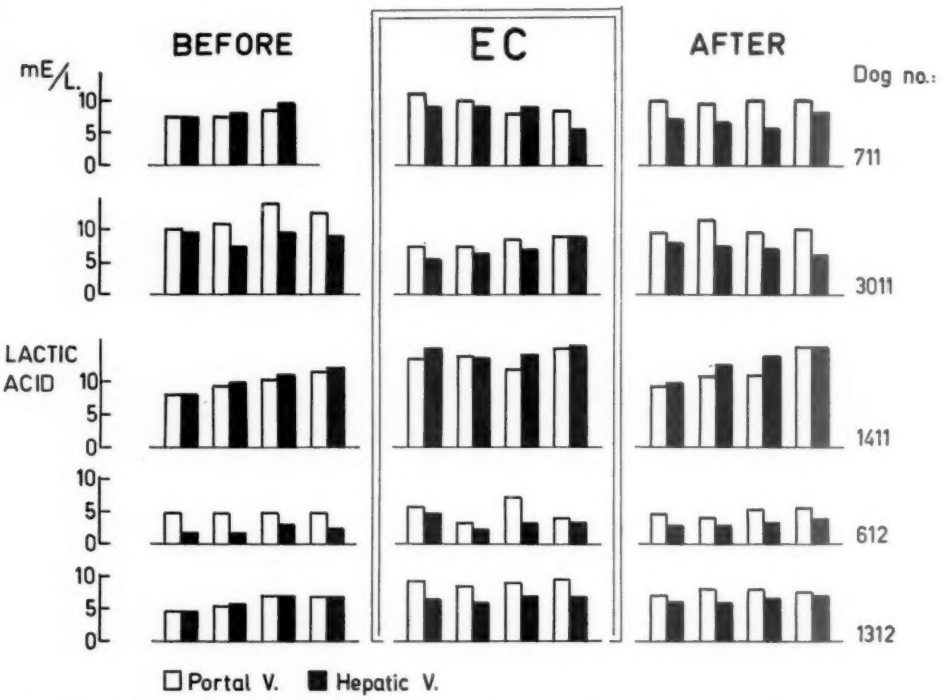

Fig. 3.—Lactic acid concentrations in portal and hepatic veins. Each pair of bars indicates samples drawn simultaneously from each source. Samples were drawn at 5-minute intervals.

The extraction rate calculated as the percentage of BSP removed from the blood in a single passage through the liver should be uninfluenced by changes in the plasma volume and other extrahepatic factors and was considered to be most reliable index of this function. Results obtained in 5 dogs are shown in Fig. 4. The extraction rate is seen to be markedly depressed during and after extracorporeal circulation.

Fig. 5 illustrates the disappearance curves for BSP in portal vein blood (essentially identical to peripheral venous blood). The flattening of disappearance curves corresponding to the previously noted decrease in extraction rate is

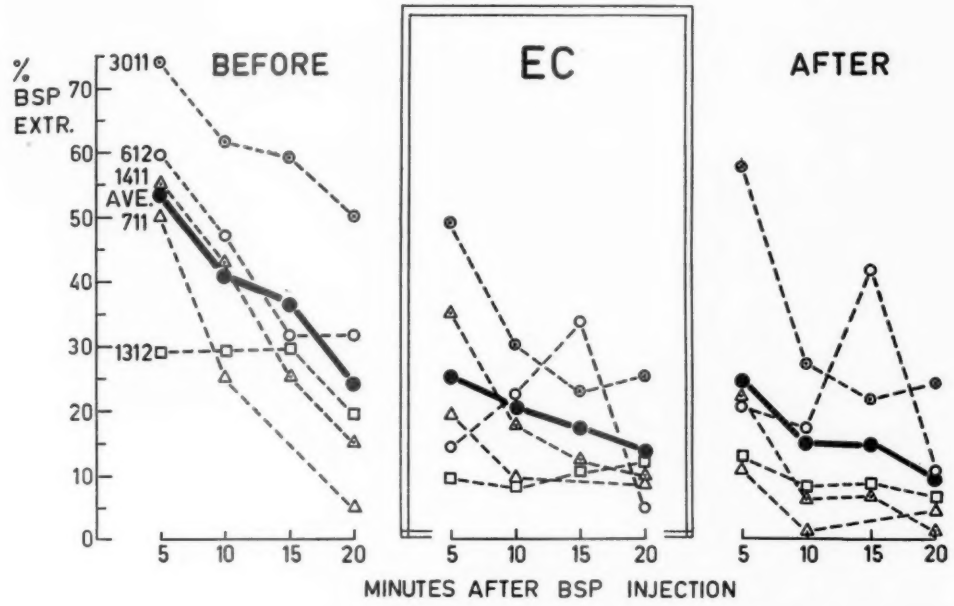

Fig. 4.—Single-passage extraction rates calculated from samples drawn simultaneously from portal and hepatic veins. Each curve represents the rate after a single injection of BSP. Curves with similar markings in each period correspond to a single experiment.

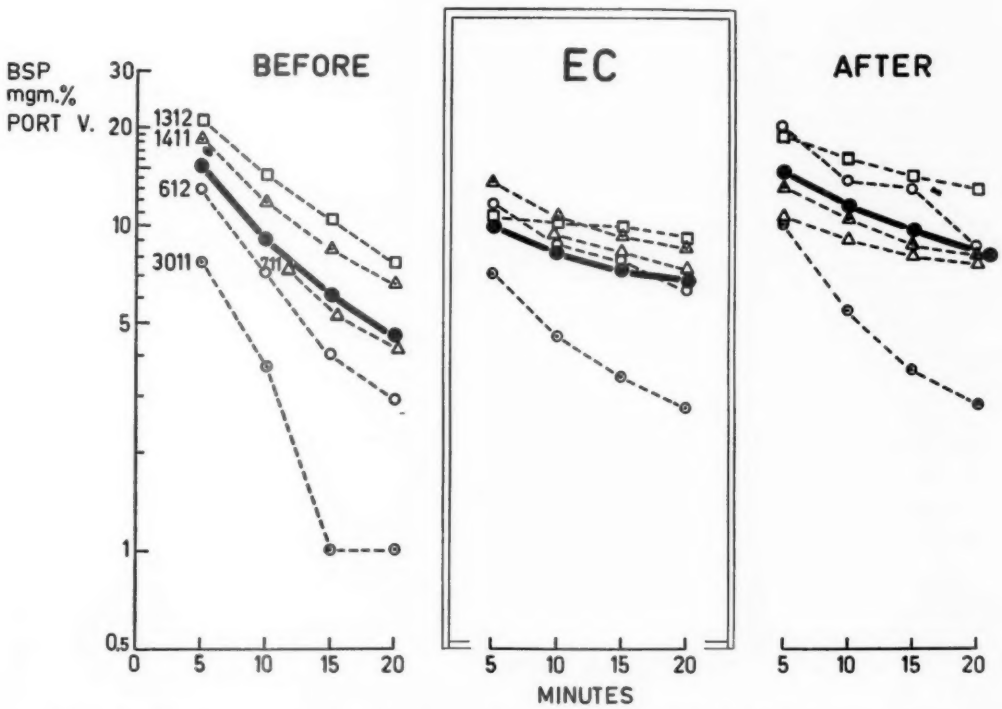

Fig. 5.—The same experiments shown in Fig. 4 but plotted in the usual manner as BSP concentration remaining in peripheral (in this case, portal) blood to illustrate disappearance rate.

evident during and after extracorporeal circulation. Half-life and plasma clearance rates are omitted for the reasons stated previously but it is obvious that half-life was markedly prolonged and plasma clearance rate reduced during and after extracorporeal circulation.

Fig. 6 illustrates single passage BSP extraction rates in control dogs given repeated injections of BSP for comparison with the extracorporeal circulation group. Although there is a tendency toward slight depression of the extraction rate with repeated tests, this is by no means as marked as that occurring during extracorporeal circulation.

It can be seen that the extraction rate changes throughout each test both in the control experiments and those with extracorporeal circulation, a circumstance at odds with the required (and commonly assumed) constant extraction rate for calculation of plasma clearance. Further investigation of this fact and other phenomena of hepatic extraction of Bromsulphalein is in progress.[11]

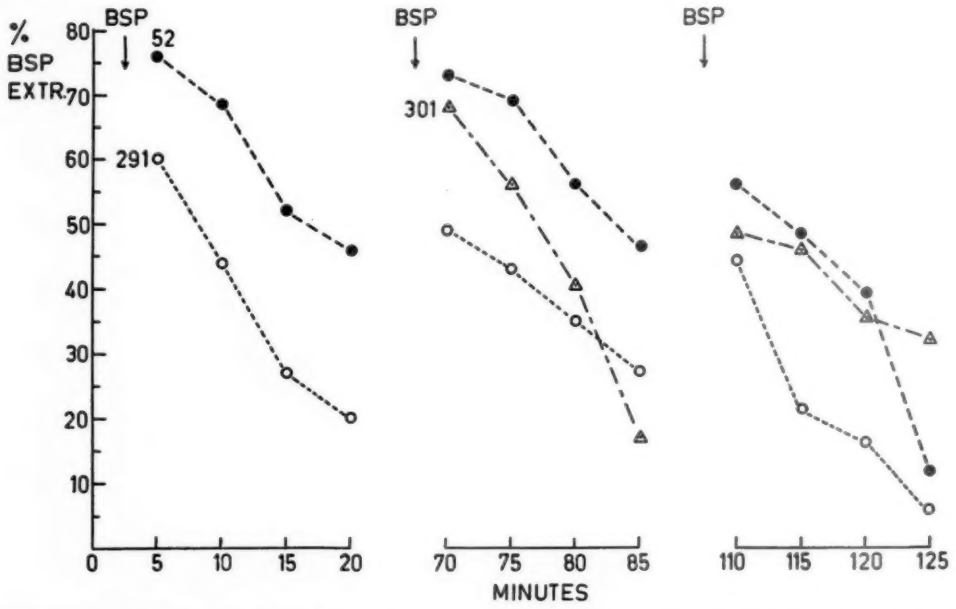

Fig. 6.—Control experiments with repeated injections. BSP injections and determinations performed at the same time intervals and in the same manner as in the experimental animals illustrated in Fig. 4.

COMMENT

The liver is known to have a high degree of susceptibility to abnormal states, especially those associated with hypoxia and hypotension. Since these conditions may be present in varying degree during extracorporeal circulation, our attention was early focused on this organ as potentially related to abnormalities in chemical balance and postoperative symptoms observed in patients operated upon with the aid of the heart-lung machine. However, definition of the functional status of such a complex organ presents obvious difficulties and most of the evidence which could be obtained only indirectly indicates the response of the liver to this circumstance.

Changes in venous pressure could be expected during periods of sudden alteration in circulatory dynamics, but the rise in portal venous pressure above the caval pressure is not readily explained. In two experiments engorgement of the splanchnic venous system was sufficient to produce distinct cyanosis of the gut and in others venous distention was readily apparent. Since after the sharp initial rise there was a progressive fall toward normal, one may speculate that this transient phenomenon is not of serious consequence. It may, however, account for the symptom of postoperative abdominal cramps observed in patients and may also contribute to the drop in arterial pressure through venous pooling and sequestration of blood.

Under normal circumstances the liver metabolizes more lactic acid than it produces. It was suspected, therefore, that in the event of a decreased level of function the liver might fail to maintain its normal rate of lactic acid withdrawal from the blood passing through and in this way contribute to the metabolic acidosis which has been observed. However, this proved not to be the case and this particular function of the liver appeared to be maintained at essentially normal levels. Concurrent observations on lactic acid levels in arterial and venous blood from various parts of the body consistently showed an elevation in blood returning from the periphery indicating the musculocutaneous system as a potential source of the increase in systemic lactic acid.

Other studies have demonstrated that the liver responds to trauma, especially hypoxia and hypotension, by liberation of potassium and is a principal source of the increased potassium levels found in shock.[15] Despite the arterial hypotension which occurred and the probability of some degree of tissue hypoxia, the systemic levels of potassium tended to fall slightly and there was no evidence of unusual potassium liberation by the liver as indicated by hepatic venous blood analysis. On this basis it would seem that the conditions of flow and oxygenation were at least within limits of tolerance by the liver for this duration of perfusion.

The significance of the depression of BSP extraction rate during extracorporeal circulation might be questioned because of the potential effect of varied concentrations of BSP in different tests and the decrease in hepatic blood flow during the period of heart-lung by-pass, each a factor which may effect the BSP extraction rate without implying an alteration in hepatic cellular integrity. Brauer and Pesotti[2] have demonstrated a decreased extraction rate when BSP concentration is increased, and Heinemann, Smythe, and Marks[7] have found a marked increase in the extraction rate accompanying a decrease in hepatic blood flow. Since in these experiments the average BSP concentration was somewhat lower and the hepatic blood flow depressed during extracorporeal circulation as compared to control periods, each factor should have tended to produce an artificial elevation of extraction rate. On these bases, therefore, the depression actually observed may have increased significance.

We have been unable to find experimental analytic studies in the literature supporting the usual assumption that the uptake of BSP by the liver is proportional to the concentration offered, that is, that the percentage of extraction during each liver passage remains constant. Qualitatively this can be reconciled

with the idea of a constant extraction rate if it is postulated that an amount of BSP proportional to the concentration in the liver is continuously returned to the blood by the liver. The high affinity of the liver to BSP[1] may support the theory of a constant percentage of extraction as long as the capacity of the liver is not reduced by exhaustion or saturation. Beyond this point of reduced capacity, accumulation of BSP in the liver may begin to permit a certain backflow into the blood. The apparent percentage of extraction would therefore represent a balance between the amount of BSP actually transferred into the liver from the blood and the amount being returned to the blood from the liver. The accumulation of BSP in the liver and the theoretic proportional reflux rate would eventually be modified by biliary excretion, but the excretory lag period[2] would probably prevent this modification during short testing periods.

In these studies it was thought desirable to duplicate conditions generally obtained during operations on humans up to this time,[5, 6] and to that end perfusion flow rates were maintained at a rather low level. Other investigations currently in progress seem to indicate definite deleterious effects of such depressed circulation, specifically in terms of oxygen utilization and metabolism.[14]

SUMMARY

Experiments were performed in dogs in an attempt to define the status of liver function during extracorporeal circulation with low flow rates. The following observations were made.

1. There was a marked, though transient, rise in portal venous pressure and a less pronounced elevation of pressure in the inferior vena cava.

2. Hepatic metabolism of lactic acid was maintained at essentially normal levels.

3. Oxygen availability did not appear sufficiently depressed to elicit any unusual potassium liberation from the liver nor to cause an elevation in systemic potassium levels.

4. Hepatic chromoexcretory function, as evidenced by Bromsulphalein extraction, was depressed during and immediately after the period of extracorporeal circulation.

5. At the flow rates used, there was a slight decrease in hepatic blood flow when compared to control levels.

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ROENTGEN SURVEY OF ASYMPTOMATIC BREASTS

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REPORT OF FIRST YEAR'S OPERATION

EARLY in 1956 we began a pilot roentgen survey of the breasts of 1,200 healthy women. A 10-year periodic roentgen follow-up of the group is planned. Our foremost objective is to bring to treatment early mammary cancers. Furthermore long-term follow-up should reveal much concerning the too little known physiologic and early pathologic changes in the female breast, especially those conditions which tend to be associated with cancer.

Women are considered acceptable for the survey if over 35 years of age. They must be clinically asymptomatic and present no dominant mass or isolated lesion in either breast. Volunteers with "lumpy breasts" or with histories of previous surgery for benign lesions are included in the study only if a recent clinical examination has shown them free of any suspicious lesion. Women in the latter group and their attending physicians have shown tremendous interest in this project.

PROCEDURE

A most important preliminary task was establishing an approach likely to be fruitful. In this we received considerable aid from Professor Katherine Boucot[1] who put her vast experience in routine chest survey work at our disposal. After a certain amount of trial and error the following procedure has been adopted.

On her first visit the volunteer receives a written explanatory message that calls attention to the experimental nature of the project, its purpose, and its mode of operation. The message stresses the importance of returning every 6 months for follow-up examinations over the 10-year period. We also instruct the woman to notify her physician immediately on discovery of any mass or change in her breasts between check-ups. As new volunteers are admitted to the survey, their records are numbered consecutively and their names are entered in a daily ledger. A questionnaire filled out by a secretary provides all pertinent information. A resident in the department examines the breasts and thyroid. His findings are recorded on a standard diagram of the breast.[6] Roentgen films of each breast are taken in both lateral and cephalocaudad positions and the technique is recorded for future reference.

Films are preferably screened by the resident who made the original clinical examination and then checked by a staff roentgenologist. A report is sent to the volunteer's physician and a duplicate is filed with the woman's record.

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The volunteer's name and address are also placed in a follow-up card file where they will automatically come to attention when re-examination is due, normally in 6 months. Should any examination be incomplete or unsatisfactory, the woman is notified and the study repeated as soon as possible.

Cases in which x-ray examination uncovers a lesion are dealt with separately. A special follow-up card is prepared and filed for review in 10 days. At that time the patient's physician is contacted. He is asked for the date of his last clinical examination and for his recommendations. If the patient has not contacted her physician, we telephone her and suggest that she do so. Where surgery is planned, we ask for a copy of the pathologic report. Should no operation be contemplated on a suspicious lesion, we ask for permission to re-examine the patient at a short interval. We make it a point to maintain contact with the woman's physician and ask to be notified of any change in her condition. Cooperation in all these matters has been extremely high.

Re-examination of all patients is scheduled and an appointment is made on the day their card comes up in the Tickler file. Pertinent events since the last visit are noted and a fresh clinical appraisal is made. Films from the previous examination are checked and the technician advised of technical improvements and of any lesions requiring special attention. A small lead shot may be placed on the skin to mark areas under special consideration.

In addition to individual folders, pertinent information is recorded in a daily ledger. This includes x-ray findings, clinical follow-up, and operation findings. Results of the x-ray examination are classified as follows:

U—Unsatisfactory study (to be repeated).
N—Negative examination, no abnormalities seen.
B—Benign dysplasia or benign lesion.
BS—Benign lesion, but resection suggested if clinically indicated.
PM—Premalignant or possible malignant lesion, resection urged.
C—Carcinoma.

The information in the ledger forms the basis of monthly or other reports. A program already in progress will transfer all patients' records to IBM cards for greater ease in statistical correlation and evaluation.

Problems commonly met in this type of work are dealt with in various ways. A volunteer who fails to keep her check-up appointment is given a new date. If there is no response she is called and her lack of interest is investigated. Every effort is made to keep the entire group under observation. However, in a few instances, periodic follow-up was discontinued because of adverse emotional reaction in the volunteer. We no longer accept highly nervous women unless they have discussed the matter with their physician.

Difficulties in dealing with an outside physician are handled by a staff member. Such problems arise from a misunderstanding and can be solved by simple explanation.

OBJECTIVES

Our major objective is detection of carcinoma in the preclinical stage. Unfortunately, by the time a lump is discovered in the breast it is often too late

for cure. Occult carcinomas with positive axillary nodes attest to the existence of nonpalpable tumors that have nevertheless metastasized. Accurate localization of occult cancers sometimes less than 0.5 cm. in diameter has been found possible by the use of roentgenography.[4] More should be learned about the earliest manifestations of carcinoma of the breast through long-term roentgen follow-up of a large group of apparently healthy women.

As long ago as 1938, Gershon-Cohen and Strickler[5] realized that the x-ray film could supplement anatomic knowledge by giving an over-all picture of the breast at different phases of its activity. Study of the variations seen in hundreds of x-ray films of normal women will go far to define what constitutes a "normal breast." Recognition of normal variations is an essential preliminary to demonstration of early neoplastic deviations.

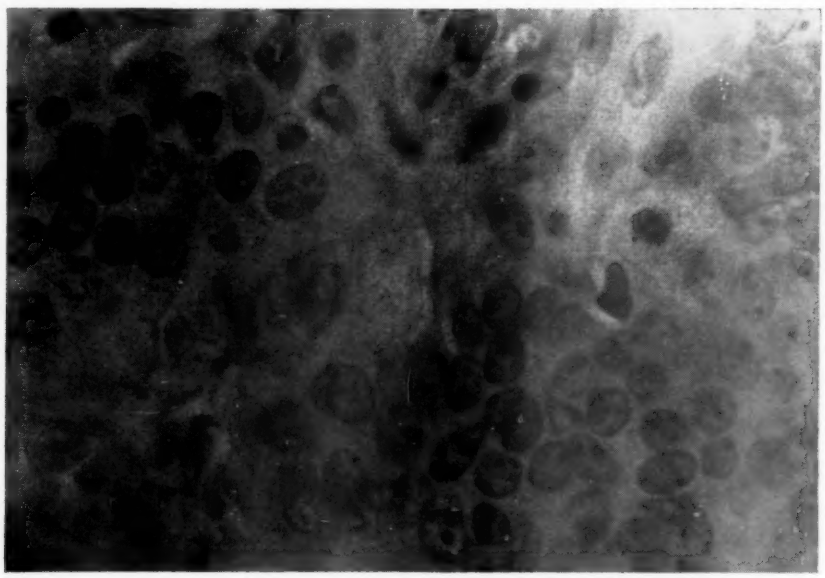

Fig. 1.—Precancerous intraductal hyperplasia. The nuclei are irregular and lack polarity. Myoepithelial cells are absent. (Case N211 paraffin section. Oil immersion 1,000 x. Courtesy of Dr. Horatio Enterlein.)

Benign mammary dysplasias and their relation to carcinoma have been the subject of much controversy. An important outcome of our long-term follow-up may be clarification of this significant point. We hope through these periodic re-examinations to follow the evolution of mammary dysplasias and give warning of impending carcinoma.

The following dysplasias claim special attention:

1. *Intraductal Hyperplasia.*—Intraductal hyperplasia, often a precancerous condition, can usually be diagnosed on the x-ray films. Because intraductal hyperplasia resembles early duct carcinoma on roentgen examination, unequivocal differentiation between it, carcinoma in situ, and early duct carcinoma is not possible at this time. Consequently we now recommend surgical removal of all lesions showing localized clustering of punctate calcifications. The following case typifies this group of lesions.

Mrs. F. F., aged 43 years, joined our survey in March, 1956. She had no symptoms referable to the breast and clinical examination was negative. The x-ray films showed a thickened duct in the lower outer quadrant of the left breast. A minute cluster of punctate calcific deposits was noted within it. A diagnosis of intraductal hyperplasia or early duct carcinoma was made. Surgical exploration was urged, but nothing was done. Seven months later the patient returned for follow-up. Clinical examination again was negative, but a definite increase in duct caliber was observed on the x-ray film. Biopsy was performed 2 weeks later. Carcinoma was suspected grossly and at frozen section, but no certain pathologic diagnosis could be given. Paraffin sections revealed precancerous intraductal hyperplasia. (Fig. 1.)

2. *Adenosis.*—Adenosis is a common finding in premenopausal women and is generally harmless. However, in a few cases malignancy does supervene.[7, 8] Two carcinomas in our survey were detected in breasts with adenosis. One is reported here in some detail.

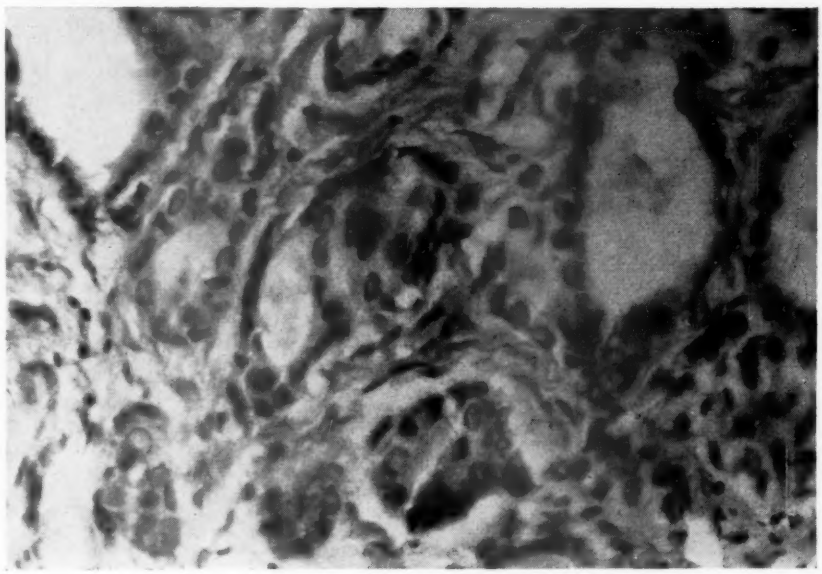

Fig. 2.—Early duct carcinoma. (Case N355 paraffin section. 4 mm. apo. 450 x. Courtesy of Dr. Charles Harris.)

Mrs. C. K., aged 45 years, joined our survey in April, 1956. She complained of severe premenstrual pain and swelling in both breasts. Two months before she had felt a tender swelling in her left breast, but this had subsided with the onset of her menstrual period. Examination by her family physician at that time revealed no masses. X-ray examination showed a small highly suspicious irregular density in the lower outer portion of the left breast. The patient was asked to return in 2 weeks for additional films and at that time, 2 days postmenstrually, a soft movable mass was palpable in the area in question. X-ray report was carcinoma and the patient was operated upon. The tumor was a duct carcinoma 1.2 cm. in diameter surrounded by an area of adenosis. There were no metastases to the axillary lymph nodes. (Fig. 2.)

3. *Macroscopic Cysts.*—We believe, with Foote and Stewart,[2] that macroscopic cysts are not precancerous. Carcinomas which occur in this type of breast usually arise in areas of adenosis distinct and apart from the cysts. However, in view of the widely differing opinions on the subject, cases with cysts will bear careful scrutiny for extended periods.

4. *Secretory Disease.*—Secretory disease[3] (the periductal mastitis of Foote and Stewart and mammary duct ectasia of Haagensen) is common and is not, as far as we know, a precancerous condition. However, it is so often seen in breasts which are also the seat of carcinoma that a long-term follow-up is imperative to rule out any connection between the two.

PRELIMINARY FINDINGS

During the first year of operation 1,102 new volunteers were examined under our survey plan. In the same period of time 581 of these patients returned for routine check-ups. Table I shows results of the roentgen examinations and operation findings. Approximately 28 per cent of all asymptomatic women were consistently reported as negative on roentgen study. Another 66 per cent had benign dysplasias or benign lesions. Adenosis predominated in the latter group and was found in the majority of women with premenstrual pain or swelling in their breasts. In the remaining 6 per cent of all examinations, one or more lesions came under roentgen suspicion. This figure was somewhat larger in the second screening than in the original because a few lesions showed evidence of growth or progression.

TABLE I. ROENTGEN AND OPERATION FINDINGS IN 1,683 SURVEY EXAMINATIONS PERFORMED IN 1956

ROENTGEN DIAGNOSIS	NUMBER OF PATIENTS		NUMBER OF PATIENTS OPERATED UPON	PATHOLOGIC REPORT		
	FIRST EXAMINATION	SECOND EXAMINATION		BENIGN	INTRADUCTAL HYPERPLASIA	CARCINOMA
Negative	315	151	–	–	–	–
Benign	730	385	6	6	0	0
Probably benign	41	29	8	6	2	0
Possible malignancy	13	15	9	3	5	1
Carcinoma	3	1	2	0	0	2
Totals	1,102	581	25*	15	7	3

*Does not include one patient reported as negative on roentgen examination and as having normal breast tissue at operation. In addition 6 patients underwent surgery but the lesions indicated as suspicious on roentgen examination were not removed at operation and were still present in postoperative x-ray studies.

Six cases reported as benign on roentgen examination were nonetheless operated upon, and benign tumors excised. Five of these patients had adenosis with small cysts; one had adenosis and early fibroadenomas. Benign tumors were also found in 6 patients where the roentgen study report was probably benign lesion, but resection was suggested if clinically indicated. Three of the 6 lesions were cysts; 2 were calcified fibroadenomas. The sixth tumor, believed to be a large cyst on the x-ray film, was not palpable clinically. Evacuation was attempted, but no fluid could be withdrawn. The patient was subsequently operated upon and a fibroadenoma removed.

Three cases were reported as possibly malignant on roentgen study. Although initial clinical examination revealed no mass, re-evaluation of the areas under roentgen suspicion clearly indicated the need for surgery. One was found to be an inflamed cyst, one was calcified fibroadenoma, and one was a patch of sclerosing adenosis. The latter tumor had moderately increased in size between x-ray examinations.

In 7 patients areas of severe localized intraductal hyperplasia detected on the roentgen film were confirmed by pathologic study. In 6 more cases surgery was undertaken, but the lesions under suspicion on the roentgen film were unfortunately not removed. None of these tumors were palpable clinically and the patients remained asymptomatic postoperatively. All 13 cases are being followed very closely both clinically and by x-ray.

One case has been reported as carcinoma on 2 successive roentgen examinations. Operation has been refused by the surgeon because of negative clinical findings. The patient is under close clinical supervision and has agreed to continue periodic roentgen follow-up.

While much has yet to be learned about roentgen diagnosis of nonpalpable breast carcinomas, 3 such tumors have already been brought to treatment as a result of our roentgen survey of asymptomatic women. The real importance of this figure lies not in the number of cancers uncovered, but rather in that these neoplasms were brought to treatment long before they would otherwise have been found. If we believe, with Urban,[9] that early diagnosis is the only controllable factor in the successful treatment of breast cancer, then our survey is worthwhile.

Every cancer has a precancerous stage. Of all breast lesions, intraductal hyperplasia is the most dangerous. In 7 of our survey patients, a small exploratory operation removed areas of severe intraductal hyperplasia. Only long-term follow-up of those patients where the lesion under roentgen suspicion was not removed will demonstrate the value of periodic roentgen examinations in the prevention of breast cancer.

SUMMARY

The procedure followed in a roentgen survey of the breast of 1,200 healthy women is described. Periodic re-examination of this group of women is planned for a 10-year period.

The foremost objective of the survey is detection of mammary cancers before they become clinically evident. Secondary goals are the establishment of roentgen criteria of normal variations and a long-term follow-up of mammary dysplasias to determine their relationship to carcinoma.

Examples are given of the diagnosis of precancerous intraductal hyperplasia and early carcinoma in 2 asymptomatic women. Roentgen and follow-up findings from the first year of this survey are tabulated.

Inauguration and partial cost defrayals of this clinic are gratefully acknowledged to Dr. Joseph C. Doane, through whose good offices this project is now receiving further assistance. Partial assistance also has come recently from a grant of the National Institutes of Health.

We gratefully acknowledge the help given us by the surgeons of the Hospital, the doctors who have so kindly cooperated by allowing us to examine their patients, the pathologists who have permitted us to use their reports, and the volunteers without whom this survey could not be conducted.

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ESTROGEN EXCRETION FOLLOWING OPERATIVE AND IRRADIATION CASTRATION IN CASES OF MAMMARY CANCER

A Preliminary Report

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ALTERATIONS in the hormonal environment of the patient with mammary cancer are known to profoundly influence the course of the disease. On the basis of laboratory experimentation and clinical observation, ablation of steroid hormone production has long been advocated for the control of advanced mammary cancer.[3] The simplest method of hormonal ablation is that of castration. Since the only side effect in the female is the production of the menopausal syndrome, castration is also the least objectionable of the ablative measures. To ablate the function of the ovaries, both surgical extirpation and irradiation have been widely used and both methods have staunch adherents.[4, 9]

Comparisons have been made of the methods of castration using as indices the rate and duration of remissions obtained with either measure.[1] Since the rationale for castration is the withdrawal of the estrogenic hormones,[2] it is logical to compare operative and irradiation castration by their efficacy in halting the endogenous production of estrogens. One acceptable method of determining the status of estrogen production in the patient is to measure the urinary excretion of estrogenic substances.[7]

It is the object of this study to compare the urinary estrogen excretion following surgical castration with that following irradiation castration in patients suffering from advanced mammary cancer. A forthcoming report will discuss additional aspects of the subject of surgical versus irradiation castration.

METHODS

Irradiation castration was obtained in accordance with the castration technique routinely used at the University Hospital. By consistent use of the standard castration technique each patient in the series so treated received a uniform and equal tissue dose of irradiation. The castration technique consists of 220 kv. radiation of h. v. l. (half value layer) 1.5 mm. Cu at a distance of 50 cm. Anterior and posterior pelvic fields measuring 12 cm. in height and 14 cm. in width are irradiated. The dosage is measured in air and varies from 1,250 to 1,575 r, depending upon the size of the patient. This dosage is divided between the 2 fields and is delivered in from 4 to 8 consecutive days. The amount of irradiation at a plane halfway between the anterior and posterior surfaces is calculated to be in excess of 625 r when using standard depth-dose tables based on unit

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density phantom material. When allowance is made for extra absorption by bone, the dose at the midplane is about 625 r. If the ovaries lie anterior or posterior to this plane, the dose received by the ovaries is proportionately greater.

Operative castration was achieved by transperitoneal bilateral oophorectomy or salpingo-oophorectomy. In either instance, removal of the ovaries was verified by microscopic examination.

The estimation of the urinary excretion of estrogen was accomplished by a modification of the method of Smith and Smith[8] utilizing acid hydrolysis of a 24-hour collection of urine followed by alkaline and ether extraction. The actual determination of estrogen in the urine is a bioassay method using spayed female rats. Results are reported in rat units (R.U.) with one rat unit being equal to the response elicited from injection of one microgram of estrone. Cornification of the vaginal epithelium in the test animals is necessary for a positive response.

Prior to making the determinations, each rat is injected with 1.5 R.U. of estradiol in 0.25 ml. of sesame oil on each of 2 consecutive days. Vaginal smears are taken on the fourth day and if vaginal cornification has occurred, the animals are considered to respond normally and are eligible for use in the bioassay. A sufficient time lapse is allowed so that vaginal smears show no residual vaginal cornification. When the test animals are satisfactory, 0.25 ml. of the unknown urine extract is injected into each of 2 rats for 2 consecutive days and again the vaginal smears are taken on the fourth day.

The interpretation as to the quantity of estrogenic substance being tested is made on the basis of the extent of vaginal cornification in the test animals. Standardizations against known quantities of estrogenic material have been previously made in the test animal group using the ratio of cornified epithelium to leukocytes and noncornified epithelium in the vaginal smear as the index of measurement. In our series, complete cornification or estrus using the extract from undiluted urine is interpreted as being equal to 2.5 R.U. For higher quantities of estrogen excretion, the 24-hour urine extract is diluted and the results obtained are multiplied by the dilution factor.

Since 2 animals are used for each determination, the final value is a total of the results obtained from each animal. However, if one animal responds with some degree of vaginal cornification while the other shows no response, the determination is discarded as invalid.

Positive results in any given animal are read from one through 2.5 R.U. based upon the original standardization with responses ranging at that time from diestrus through metestrus. Because one microgram of estrone (1 R.U.) has been used at the time of the standardization, the unknown material that fails to induce vaginal cornification can only be interpreted to be less than 1 R.U. in amount. However, the extracts are divided between 2 test animals, so that the lowest possible reading is reported as "less than 2 R.U." In some cases, an occasional cornified vaginal epithelial cell is found and this is reported as "less than 2 R.U.—trace" indicating some small degree of estrogenic activity.

MATERIAL

To date, 11 women with mammary cancer have been selected for castration and study. These patients all had far-advanced mammary cancer and were selected for castration because of their premenopausal status, or because they exhibited significant amounts of urinary estrogen by bioassay or showed evidence of estrogen stimulation of the vaginal mucosa on Mack stain. One premenopausal patient (D. M.) excreted only 2 R.U. of estrogen in 24 hours prior to castration in a single determination. Since this patient was menstruating regularly, it was assumed that this minimal excretion of estrogen represented an early portion of the ovulatory cycle in which estrogen excretion is characteristically low. Unfortunately, her clinical condition demanded early oophorectomy and precluded a second preoperative determination.

Of the 11 patients selected for castration, 10 were white Caucasians and one was an American Indian. In none of the patients was there a history of estrogen administration immediately before or during the period of study.

The choice of the method of castration was made on the basis of clinical condition, convenience, and personal preference of the attending physician.

The menstrual status of the group was as follows: 7 were premenopausal, menstruating regularly; one was postmenopausal for more than 5 years; and 2 had previously undergone hysterectomies for benign conditions. Of this latter group, one patient had experienced "hot flushes" following hysterectomy, and the other had no menopausal symptoms. One patient had noted scanty, irregular menstrual periods without evidence of the menopausal syndrome and was, therefore, considered premenopausal.

The average age of the group was 44.6 years. The youngest patient was 36.8 years, and the oldest was 59.4 years. The patients who underwent operative castration average 46.4 years of age and those castrated by irradiation average 42.6 years.

Tables I and II summarize the age and menstrual status of the patients studied.

Table I. Age and Menstrual Status of Surgically Castrated Patients

PATIENT	AGE	MENSTRUAL STATUS
L. G.	47.8	Premenopausal
V. M.	59.4	Postmenopausal
D. M.	40.8	Premenopausal
I. P.	36.8	Premenopausal
L. W.	55.9	Previous hysterectomy
M. J.	37.4	Previous hysterectomy
	46.4—Average of surgically castrated	

Table II. Age and Menstrual Status of X-Ray Castrated Patients

PATIENT	AGE	MENSTRUAL STATUS
D. A.	40.9	Premenopausal
T. M.	46.4	Premenopausal
J. P.	44.4	Premenopausal
M. R.	40.8	Premenopausal
R. M.	43.1	Premenopausal
	42.6—Average of x-ray castrated	

RESULTS

Regardless of the mode of castration, all patients studied showed an eventual drop in estrogen excretion from precastration levels. In all patients but one (J. P.) the level declined eventually to what was considered negligible quantities of estrogen, that is, 2 R.U. or less of estrogen excreted in 24 hours. In no patient was there seen a rise in estrogen excretion within the period of the study, which in 5 cases extended more than 120 days after castration.

Irradiation Castration.—In 4 of the 5 cases studied, estrogen excretion reached negligible levels within 130 days after conclusion of the castrating dose of x-ray. In the remaining case, there was a significant decrease from the pretreatment level.

Of the 5 patients studied, one demonstrated a decline in estrogen excretion to less than 2 R.U. per 24 hours in less than 60 days after completion of irradiation. Three patients showed a decrease to negligible estrogen excretion within a period of 80 to 130 days after the termination of irradiation.

The eventual decline in estrogen excretion was not a gradual one over the period of observation, but was relatively precipitous, usually dropping from pretreatment levels within a 30-day period.

No consistent relationship was demonstrated between age or menstrual status and the time interval from irradiation to the fall of the estrogen excretion.

Surgical Castration.—In the 6 patients of the series who underwent surgical castration, urinary estrogen excretion had fallen to negligible levels by the termination of the period of observation. One patient (D. M.) had relatively low estrogen excretion preoperatively, but was menstruating regularly at the time of admission to the hospital and was assumed to have a normally high estrogen production and excretion.

In no patient did the rate of estrogen excretion rise during the period of the study. In all cases, this period was over 45 days, and in 5 cases the study was in excess of 60 days, over 90 days in 3 cases, and over 120 days in one case.

In 4 of the 6 patients estrogen excretion decreased to a level below the lowest limits of measurement within a period of 9 days after surgical castration. One patient showed a small (2.5 R.U.) amount of urinary estrogen after 9 days. This was, however, a substantial decrease from the preoperative rate of 10 R.U. per 24 hours. In the remaining patient, urinary estrogen was not measured within the 9-day period.

In the 5 patients who were studied at frequent intervals after castration, estrogen excretion dropped to less than 2 R.U. within 5 days after castration.

In the 2 patients studied 2 and 3 days after operation, there was negligible urinary estrogen excretion at this early date.

The one patient who had sustained significant estrogen excretion later than 9 days following oophorectomy was postmenopausal. All other patients in this series were either premenopausal or had undergone hysterectomy.

Patient (M. J.), who had undergone hysterectomy and had experienced "hot flushes" prior to castration, showed a decrease in estrogen excretion from 10 R.U. preoperatively to less than 2 R.U. in 24 hours postoperatively.

TABLE III. ESTROGEN EXCRETION FOLLOWING IRRADIATION CASTRATION

PATIENT	AGE IN YEARS	MENSTRUAL STATUS	PRECASTRATION ESTROGEN EXCRETION IN R.U./24 HOURS	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170
D. A.	40.9	Premenopause	Menstruating							8 (87)*		<2 (105)					<2 (162)	
T. M.	46.4	Premenopause	10	10 (33)					10 (80)		10 (108)			<2 (136)				
J. P.	44.4	Premenopause	10				8 (64)								4 (147)			
M. R.	40.8	Premenopause	8						6 (79)				2 (123)					
R. M.	43.1	Premenopause	Menstruating			<2 (56)		<2 (71)										

*Exact date of urine collection.

TABLE IV. ESTROGEN EXCRETION FOLLOWING SURGICAL CASTRATION

PATIENT	AGE IN YEARS	MENSTRUAL STATUS	PRECASTRATION ESTROGEN EXCRETION IN R.U./24 HOURS	DAYS POSTOPERATIVE 2	3	4	5	6	7	8	9	10	20	30	40	50	60	70	80	90	100	110	120	130
L. G.	47.8	Premenopausal	10			<2	<2												<2 (73)*					
V. M.	59.4	Postmenopausal	10		5	2.5		2			2.5			2.5 (34)						<2 (98)				
D. M.	40.8	Premenopausal	2†		<2		<2		<2									<2 (69)					<2 (123)	
I. P.	36.8	Premenopausal	10		2										<2 (42)	<2 (45)								
L. W.	55.9	Previous hysterectomy	6	<2			<2								<2 (41)	<2 (51)								
M. J.	37.4	Previous hysterectomy	10												<2 (41)							<2 (115)		

*Exact date of urine collection.
†Menstruating regularly; assumed high estrogen excretion.

Pre- and postcastration urinary estrogen determinations in each patient are graphically summarized in Tables III and IV.

DISCUSSION

The technique of measuring the urinary estrogen excretion by bioassay obviously does not take into account circulating estrogenic material; in addition, the technique is subject to the many vagaries usually associated with bioassay. Although an excretion of less than 2 R.U. in 24 hours may mean that there is no estrogen excretion, we cannot definitely say that minute amounts of estrogen are not excreted in the urine and that these may represent a larger or more physiologically active fraction available in vivo. In cases where the rate of excretion was less than 2 R.U. of estrogenic substance per day, we have arbitrarily referred to this excretion as negligible rather than nonexistent. Based upon our standardization curves, we regularly report values as low as one rat unit in any given animal. However, since the daily urine extract is divided between 2 test animals, excretions below one rat unit in each animal are reported as "less than 2 R.U." That is, since there is no response we can only say that one-half of the urine extract contained less than one rat unit of estrogenic substance. A small nonmeasurable response occasioned by the appearance of a few cornified vaginal epithelial cells in the test smear is reported as "less than 2 R.U.—trace." It should be remembered that less than 2 R.U. represents an extremely small fraction of estrogenic material, an amount physiologically less active than 2 mcg. of estrone.

As judged by serial determinations of estrogen excretion in mammary cancer patients following both operative and irradiation castration, it would appear that both means are effective in ablating ovarian function.

Surgical castration results in a rapid fall of urinary estrogen, often to less than 2 R.U. per 24 hours, usually within 2 to 3 days after castration. X-ray castration, although eventually successful in reducing the urinary estrogen, is a slower process. There appears to be a variable latent period of 2 to 4 months before the irradiated ovaries cease to produce estrogenic substances. In our series, the time interval between the termination of irradiation and fall in urinary estrogen was usually 80 to 130 days. However, estrogen output in one patient persisted at significant levels for 147 days. In another patient, however, who was assumed to be actively excreting estrogen as a premenopausal woman, estrogen output fell some time prior to 56 days after irradiation.

The criticism that ovarian ablation accomplished by irradiation may not be immediately reflected in the urinary output of estrogen is answered by the rapid fall of urinary estrogen following operative removal of the ovaries.

Figs. 1 and 2 show typical responses to operative and x-ray castration with urinary estrogen determinations plotted against the time of the determination after castration.

We have not been able to demonstrate in this study the often-referred-to correlation between the premenopausal or "young ovaries" and the necessity

for larger amounts of irradiation to obtain castration.[6] Likewise, there was no correlation between the age of the patient and the time required for a significant fall in urinary estrogens following irradiation.

The case of Patient M. J., who had experienced "hot flushes" following hysterectomy and then showed a decrease from 10 R.U. of estrogen excretion to less than 2 following castration, points out the fallacy of considering the history of "hot flushes" as adequate proof of ovarian inactivity. Indeed, in several other patients not included in this series, we have found significant amounts of urinary estrogen despite a history of "hot flushes."

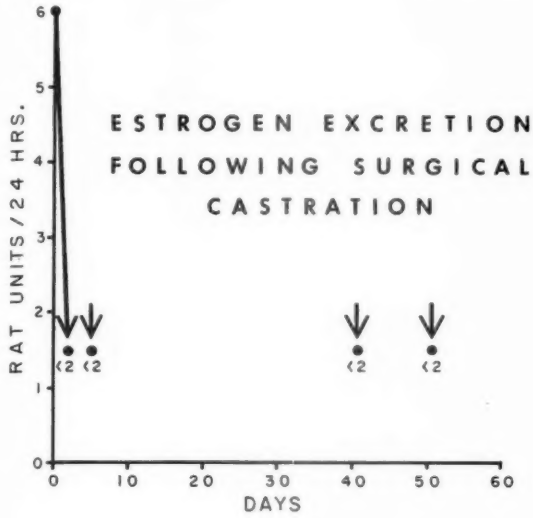

Fig. 1.

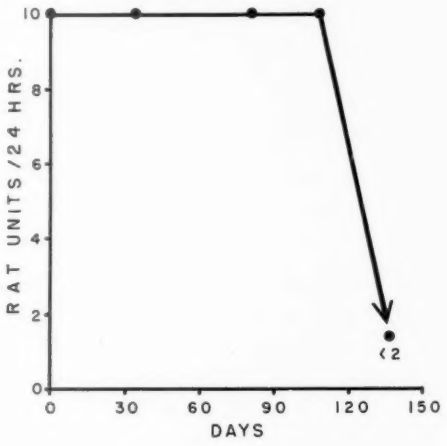

Fig. 2.

Fig. 1.—Estrogen excretion following surgical castration.
Fig. 2.—Estrogen excretion following irradiation castration.

The case of Patient V. M. represents ovarian activity in a postmenopausal patient more than 5 years past the menopause. This patient, prior to oophorectomy, excreted 10 R.U. of estrogen in the urine per day. Following castration, the excretion progressively fell to insignificant levels. As pointed out by Lemon and others,[5, 10] the syndrome of postmenopausal ovarian hyperplasia is not a rare entity and does result in significant estrogen production. In this case, microscopic examination of the ovaries removed at operation did not show thecal hyperplasia, but, nevertheless, we are confronted by falling estrogen excretion in a postmenopausal patient following castration. This observation places on tenuous and dangerous ground the assumption that patients 5 or more years past the menopause cease to have ovarian function.

SUMMARY

Eleven women patients suffering from far-advanced mammary cancer were castrated using either operative removal of the ovaries or x-ray irradiation to the ovaries as the mode of castration. The urinary excretion of estrogens was determined by bioassay before and following castration. On the basis of these observations, x-ray and surgical castration are discussed as to the efficacy and

the time required for castration. The lack of correlation between the history of "hot flushes" and estrogen excretion is pointed out as well as a finding of significant urinary estrogen levels in patients more than 5 years past the menopause.

CONCLUSIONS

1. Both surgical castration and x-ray irradiation are effective in ablating ovarian function as judged by the urinary estrogen excretion.

2. Surgical castration reduces the urinary excretion of estrogen to very low levels within a short period of time. The estrogen excretion often falls below the level of measurement within 48 to 72 hours after castration.

3. X-ray irradiation to the ovaries reduces the urinary excretion of estrogen to extremely low or negligible levels after a prolonged latent period. This latent period is usually 80 to 130 days, but may be over 140 days.

4. A history of "hot flushes" does not necessarily mean that the ovaries have ceased to produce estrogenic substances.

5. Postmenopausal patients 5 or more years past the menopause may still secrete significant amounts of ovarian estrogen.

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THE MANAGEMENT OF PAPILLARY CARCINOMA OF THE THYROID GLAND

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PAPILLARY carcinoma is the most commonly occurring type of carcinoma in the thyroid gland. It possesses a better prognosis than any other form of carcinoma of that organ, although the degree of malignancy varies widely among a group of cases. In some patients the disease is virulent enough to kill within a few months; in others it grows so slowly that even with bony or pulmonary metastases the patient is able to continue normal activity for many years. The pathologic picture presented also varies. Pure types do not always occur, and a mixture of papillary and follicular elements is often encountered.

As one peruses the literature on this subject, it is evident that there is almost total agreement that radiation therapy is not effective in treating this entity, and there is considerable disagreement over what type of surgery should be performed. Also, one is impressed with the wide range of end results. The variable natural course of the disease and the difficulty in evaluating the cytologic pattern apparently contributes significantly to the difference in results.

The surgical treatment advocated varies from simple enucleation to total thyroidectomy for the primary lesion and from doing nothing to radical neck dissection for the regional node bearing areas.

Our method of treatment is influenced by the prognosis of the disease and by the frequency of cervical node involvement.

PROGNOSIS

It has been stated that the over-all prognosis of this disease is better than any other carcinoma of the thyroid gland. The fact remains that it is a malignant tumor, it does metastasize distantly, and it does kill people. In Martin's series[6] of 180 determinate patients there were 38 per cent failures in a 5-year survival period. Thirty-three, or more than half the failures, died during the 5-year period and often with widely disseminated disease. Horn and Dull[5] presented a smaller series wherein 31 per cent failures were noted in the 5-year survival rate and 45 per cent died within 12 years. In Crile's series,[3] which is the most optimistic, there is a 13 per cent mortality rate.

CERVICAL NODE INVOLVEMENT

A careful study of regional lymph nodes was made and reported in a recent paper by Frazell and Foote.[4] From 1946 through 1953, 182 specimens of radical neck dissection for papillary carcinoma were examined. They reported an over-all cervical node involvement of 84.6 per cent. If the necks

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were clinically positive or suspicious for metastases the rate was 96 per cent, and if the necks were clinically negative 61.2 per cent of the patients were found to have positive nodes. Approximately 50 per cent of these nodes were found to implicate the middle and superior jugular vein areas.

METHOD OF TREATMENT

Our advocated method of treatment for this disease is as follows. If a patient presents a lump in the thyroid gland and especially if there has been recent increase in size, surgical excision is advised. A total lobectomy is performed and immediate frozen section obtained. Precaution is taken not to cut into tumor tissue, and the total lobe is sectioned after it is removed from the surgical field. If a diagnosis of papillary carcinoma is made, the usual exposure is obtained for a total radical neck dissection on the same side, whether or not nodes are palpable. The strap muscles are removed with the neck dissection specimen.

If a patient primarily presents a node in the neck, an aspiration biopsy is performed on it, whether or not a mass is palpable or suspected in the thyroid gland. If a diagnosis of metastatic papillary carcinoma from the thyroid gland is made, the patient is subjected to radical neck dissection and resection of the strap muscles, the homolateral thyroid lobe, and isthmus. A radical neck dissection is advocated for patients who develop cervical metastases subsequent to control of the primary lesion.

We prefer to treat this lesion as a genuine cancer because it does cause people to die and because such a high percentage of positive nodes are present in the neck, even though they are not detected preoperatively.

There has been some definite opposition expressed to this method of treatment. The arguments are based on resulting cosmetic deformity, morbidity of neck dissection, inadequacy of neck dissection, and the supposition that desiccated thyroid is a curative agent for this disease.

Cosmetic Deformity.—The scars resulting from a radical neck dissection incision are admittedly more noticeable than if surgery had not been performed. However, the deformity and scarring are not too great and are definitely compatible with normal living. We know that a high percentage of papillary carcinomas of the thyroid gland do metastasize to the neck. In view of the fact that this is a definite malignant process which may ultimately cause death, the scars resulting from a radical neck dissection are a small price to pay for the control of the disease. Certainly there are cases in the 13 to 38 per cent mortality, depending upon whose figures you rely, that might have been salvaged with radical neck dissection. They would have tolerated deformity many times better than their eventual fate.

Morbidity of Neck Dissection.—The operative mortality in performing this operation is less than one per cent,[7] but there is other morbidity to be considered. Since the spinal accessory nerve should be sacrificed in each patient, there is some drooping of the shoulder as a result of wasting of the trapezius muscle. The patient sometimes has slight difficulty in externally

rotating the shoulder; for example, in slipping on his coat. However, with physiotherapy and usage these patients do develop well-functioning shoulders and practically any function which was originally performed can be reclaimed with time. Occasionally the cervical branch of the facial nerve is damaged with resultant partial drooping of the lower lip. These items of morbidity, although a nuisance to the patient, certainly are not insurmountable difficulties and are justifiable if we admit we are dealing with a malignant process.

Inadequacy of Neck Dissection.—It was stated in a recent publication[2] that the conventional neck dissection is an inadequate procedure. Although it is known that some of the lymphatics extend into the mediastinum it is certainly more than coincidence that most of the metastases are found in the neck. Perhaps the author of that article is debating theoretical rather than practical factors. In studying neck metastases in a large group of cases it was revealed that approximately 50 per cent of the metastases were found to involve the middle and upper jugular chain of nodes, while 33 per cent involved the lower jugular nodes. These figures would indicate that most of the lymphatics must travel along the superior and middle thyroid veins which empty into the deep jugular vein. There are lymphatics spreading along the inferior thyroid veins; however, it must be remembered that the lymphatic drainage which travels toward the mediastinum eventually ends in the thoracic duct. This apparently accounts for the fact that most of the metastases eventually lodge in the neck and is the reason they are extremely seldom found in the mediastinum.

Relation of Desiccated Thyroid to Papillary Carcinoma.—A number of investigators have shown thyroid dependency in isolated cases of this type of thyroid carcinoma.[1, 2, 8] There are accounts of patients with pulmonary and osseous metastases treated with desiccated thyroid with definite regression of lesions and apparent arrest of the disease. There are also others in which no beneficial effects have been noted by the administration of this medication.

Thomas[9] has recently reviewed the literature on this subject and found case histories of patients treated for thyroid cancer with desiccated thyroid as early as 1896. Twenty-two patients presenting papillary type carcinoma were treated with 3 to 5 grains of thyroid daily. Some had cervical node metastases, some bony, and others pulmonary involvement. Six of these did not respond to the treatment at all and 13 responded in varying degrees, from a little improvement to complete disappearance of distal metastases. Three demonstrated regression at first followed by later progression of disease and death.

There is no doubt that desiccated thyroid has an influence on some cases of this disease. How permanent the effect is, no one is qualified to say at present.

DISCUSSION

There are many reasons why there is discrepancy in the end results reported by different writers. The number of cases reported by some are too small to be significant. The length of follow-up report is seldom long enough since this disease runs such a variable course. The pathologic picture of

thyroid cancer is so variable that the writers must include different types of material in their series. For example, Crile[3] states that the cases are placed in the category of highest malignancy and that an inoperable patient is never seen. This is in contrast to Frazell,[4] who talks of the many cases that are nonsurgical because of extensive involvement when first seen. The more conservative workers with this disease are somewhat ambiguous in their surgical management. A definite point is made that complete excision of the primary lesion is so necessary for cure and that either biopsy or subtotal resection may lead to hopeless recurrence. Here, good cancer surgical principles are adhered to. Apparently, they do not believe that this same principle applies to the management of neck metastases. Certainly lymphatic channels are transected, some of which must contain cancer cells, in performing the limited excision of nodes. In explaining why this inadequate neck surgery is possible without spread of the process occurring, a vague allusion is made to the possibility that desiccated thyroid protects against such a happening. It is odd that the medication would be protective in the neck but not in the thyroid area. Even if the desiccated thyroid offered this protection in the neck it would seem reasonable to expect that it would be ineffective in many cases, since it has been shown that many cases of papillary cancer do not respond to this agent.

In reviewing this material, I have been impressed by the fact that often when this subject is discussed so many factors are introduced that it must be confusing for the reader. The argument of what to do about a thyroid nodule, the statistical comparative infrequent occurrence of deaths from thyroid cancer, the fallacy of neck dissection, the emotional argument of "altering lives of girls and young women by mutilating operations," and other exaggerated statements concerning morbidity of neck dissection all serve to detract from the main thesis. I believe the problem should be presented as a clear-cut issue: Is papillary carcinoma a type of malignant disease which will kill people? Does the conservative method of treatment, using desiccated thyroid, control patients indefinitely? The answer to the first question, of course, is affirmative. The answer to the second is negative. No one has had experience of sufficient duration to know how long a papillary carcinoma remains thyroid dependent. There is concrete evidence that a high percentage of such tumors do not respond at all and that a portion of those responding at first lose their thyroid dependency if treated long enough and eventually cause death.

It would seem risky then to subject otherwise surgically resectable cases to this type of treatment per primam, not knowing what the long-term effect will be in any one case. It would be comparable to initially treating all primary cancers of the breast with testosterone and foregoing the possibility of cure instead of prescribing androgens only for patients with advanced spread who are beyond the state of being salvaged.

Those who resect obviously enlarged nodes through a thyroidectomy incision cannot remove all the tumor tissue which is present in the neck. Figures elsewhere in this paper indicated that 50 per cent of the cervical metastases were located above the level of the mid-jugular area. Positive nodes are left

in approximately 60 per cent of the patients upon whom neck surgery is not performed. In view of the present knowledge of the effect of desiccated thyroid, and especially the variability in response, it would seem negligent not to at least attempt the removal of all metastases in the neck when there is no evidence of further spread of the disease. It would seem more rational to subject such patients to radical neck dissection and to use desiccated thyroid when distant metastases appear.

SUMMARY

Papillary carcinoma is the most common malignant tumor of the thyroid gland and has a better prognosis than other thyroid cancers. It metastasizes frequently to the cervical lymph nodes and may spread to bone and lungs.

Some cases are thyroid dependent and can be kept under control for a long time, in spite of metastases; others do not respond at all or respond temporarily and then progress to fatal termination.

Since this disease causes definite mortality and the response to thyroid hormone is so variable, it would seem reasonable that localized disease in the neck be treated with curative intent by adequate surgery.

Our advocated treatment is thyroid lobectomy plus homolateral radical neck dissection whether or not palpable lymph nodes are present.

It is recommended that desiccated thyroid therapy, at least in our present state of knowledge, be kept under continuous study and be reserved for patients with nonresectable disease.

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THE EFFECT OF THE SITE OF TRANSPLANTATION AND PRESENCE OF GLANDULAR DEFICIENCY ON THE SUCCESS OF THYROID AUTOGRAFTS

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WITHIN the past few years, some of the immunologic mechanisms underlying homograft rejection have been elucidated. Investigations are being carried out in many directions in order to achieve permanent survival of transplanted tissues and organs following surgery. While the development of a means of interference with the antigen-antibody reaction responsible for the rejection of a graft is most important, there are many other factors which must be better understood before homografting will be feasible in patients. One of these is the effect of the transplantation site on the viability and function of a graft. Another is the significance of a pre-existing glandular deficiency on the ultimate fate of the graft. A knowledge of the degree of importance to place upon these factors when contemplating the homotransplantation of tissue is mandatory.

Halsted's often-quoted law of deficiency, that a graft will not survive unless the host animal has a physiologic need for it, was originally postulated in reference to results obtained with autotransplants.[3] He was working with auto- and homotransplants of parathyroid glands in dogs and transplanting them to the thyroid gland and rectus abdominis. Regardless whether a deficiency had first been created or not, none of the homotransplants were successful. The parathyroid autotransplants were successful only if there was simultaneous excision of at least 3 parathyroid glands. If only 2 parathyroid glands had been removed, that is, if the deficiency did not exceed one half of the total amount of glandular tissue, the parathyroid autografts were always promptly absorbed. From these studies, Halsted concluded that a considerable degree of deficiency is essential to the success of transplantation.

Since this theory was originally postulated, numerous investigators, Ingle,[5] Wyman,[11] Lux,[8] Eaken,[4] Jones,[6] Deanesly,[2] and others, have continued to believe that a deficiency plays a significant role in the survival of homo- as well as autotransplants. Ingle,[5] in a study of autotransplantation and regeneration of the adrenal gland, transplanted whole adrenal glands and adrenal capsules to the ovaries of rats. Some of his recipient animals had one adrenal gland intact; others had had total adrenalectomy prior to autotransplantation. Several weeks after grafting, upon histologic examination of the transplant, he

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found a rim of surviving cortical cells in the rats having one adrenal gland in situ. In the animals in which both glands had been removed, a much greater proliferation of cortical cells was seen on sections. The author concluded that survival of an adrenal autograft depends upon the presence of a capsule and, in addition, upon a physiologic need for the principle elaborated by the adrenal gland. However, it should be noted that viable cortical cells were present in both series of animals. More recently, Liddle,[7] studying thyroid and adrenal transplants in dogs without glandular deficiency, concluded that a need by the body was not necessary for successful autotransplantation of glandular tissue. He obtained histologic takes of thyroid autografts following transplantation to brain, liver, spleen, and muscle even in the absence of the pituitary gland in some of the dogs. In a few, he demonstrated glandular function with uptake of radioactive iodine but felt that there was a lag of several months between histologic take and hormone function.

In this study, the effect of different sites of transplantation and of glandular deficiency on the take of a graft were evaluated following autotransplantation of rabbit thyroid. Autologous gland was utilized in order to avoid the complication of immunologic incompatibility which would have been present if homologous tissue had been used instead.

METHOD

Mixed strains of stock adult rabbits were used. Originally 4 sites of transplantation were to be tested: the renal capsule, the subserosa of the stomach, the sheath of the rectus abdominis, and the bone marrow. It was found that implantation of tissue in the marrow cavities of a rabbit was not feasible, even in the region of the iliac crest which was somewhat larger than other contemplated areas. Therefore this site was discarded after one trial. Thyroid tissue was selected for transplantation, since it was possible to easily measure its function by uptake of radioactive iodine, I^{131}, in addition to examining it histologically.

It was thought that creation of a thyroid deficiency might favorably alter the outcome of these grafts. However, it was found to be technically difficult to perform a total thyroidectomy without removal of the parathyroids. The postoperative mortality from subsequent tetany was so high that after the first few preparations were completed, only a hemithyroidectomy was performed in the remainder of the animals in this series.

In each case, the rabbit was anesthetized with IV Nembutal. The thyroid gland was removed under sterile conditions, washed in saline, and cut into slices approximately 1 to 1.5 mm. in thickness. All the fragments from one lobe of the gland were then implanted into the selected site.

To Rectus Sheath.—A total thyroidectomy was performed on 5 rabbits. Hemithyroidectomy was performed on 2 rabbits. The rabbit's own thyroid, now cut into small fragments, was implanted with forceps into a pocket in the rectus sheath.

To Renal Capsule.—Total thyroidectomy was performed on 4 rabbits and hemithyroidectomy on another 4 rabbits. A slit was made on the midanterior surface of the renal capsule and a pocket was created under the capsule. Care was taken not to traumatize the renal parenchyma. The fragments of one autologous thyroid lobe were implanted into the pocket and the capsule was closed.

To Subserosa of the Stomach.—A hemithyroidectomy was performed on 5 rabbits. A tunnel was created beneath the serosa of the stomach; care was taken not to perforate the mucosa. The autologous fragments of thyroid tissue were implanted into this pocket.

To Subcutaneous Tissue.—A hemithyroidectomy was performed in one rabbit. An incision was made over the right iliac crest. An attempt was made to implant thyroid slices into a cavity created with a knife. Most of the fragments were extruded and lay scattered about the iliac crest in a relatively avascular area. The incision was closed.

After one month had elapsed following transplantation, radioactive iodine was administered to all the surviving rabbits. Twenty-four hours later, each rabbit was sacrificed and the I^{131} uptake determined. Initially variable dosages were administered ranging from 5 to 100 μc. It was found that a 5 μc dose was adequate and this amount was used thereafter. A block of tissue in the region of the autologous thyroid transplant was removed. The area could be identified by the nonabsorbable cotton sutures. Grossly, small pinkish nodules could be seen studding the surface of the kidney. In the other sites, no tissue was grossly evident. The tissue was immediately placed in a DS-3 well scintillation Geiger counter and counts were taken. Background counts and control counts of tissue from the other kidney were also obtained.

RESULTS AND DISCUSSION

Since it was not possible to isolate the thyroid fragments from the surrounding tissue to obtain counts per unit weight of tissue, quantitation of the counts was not meaningful. Qualitatively, however, the results were clear enough so that conclusions could be drawn.

Thus, in the case of the 5 surviving rabbits following transplantation to the kidney, background count was 100/min., the uptake on a block of tissue from the control kidney without thyroid was <300/min. above background. The results on the renal tissue with thyroid implanted beneath the capsule are shown in Table I.

The other 3 rabbits in the series died of tetany postoperatively.

TABLE I

RABBIT	DOSE	OPERATIVE PROCEDURE	COUNTS/MIN.
B1	50 μc	Total thyroidectomy	50,800
B2	5	Hemithyroidectomy	34,500
B3	100	Hemithyroidectomy	40,500
B4	50	Hemithyroidectomy	38,200
B5	50	Subtotal bilateral thyroidectomy	29,100

Fig. 1.

Fig. 2.

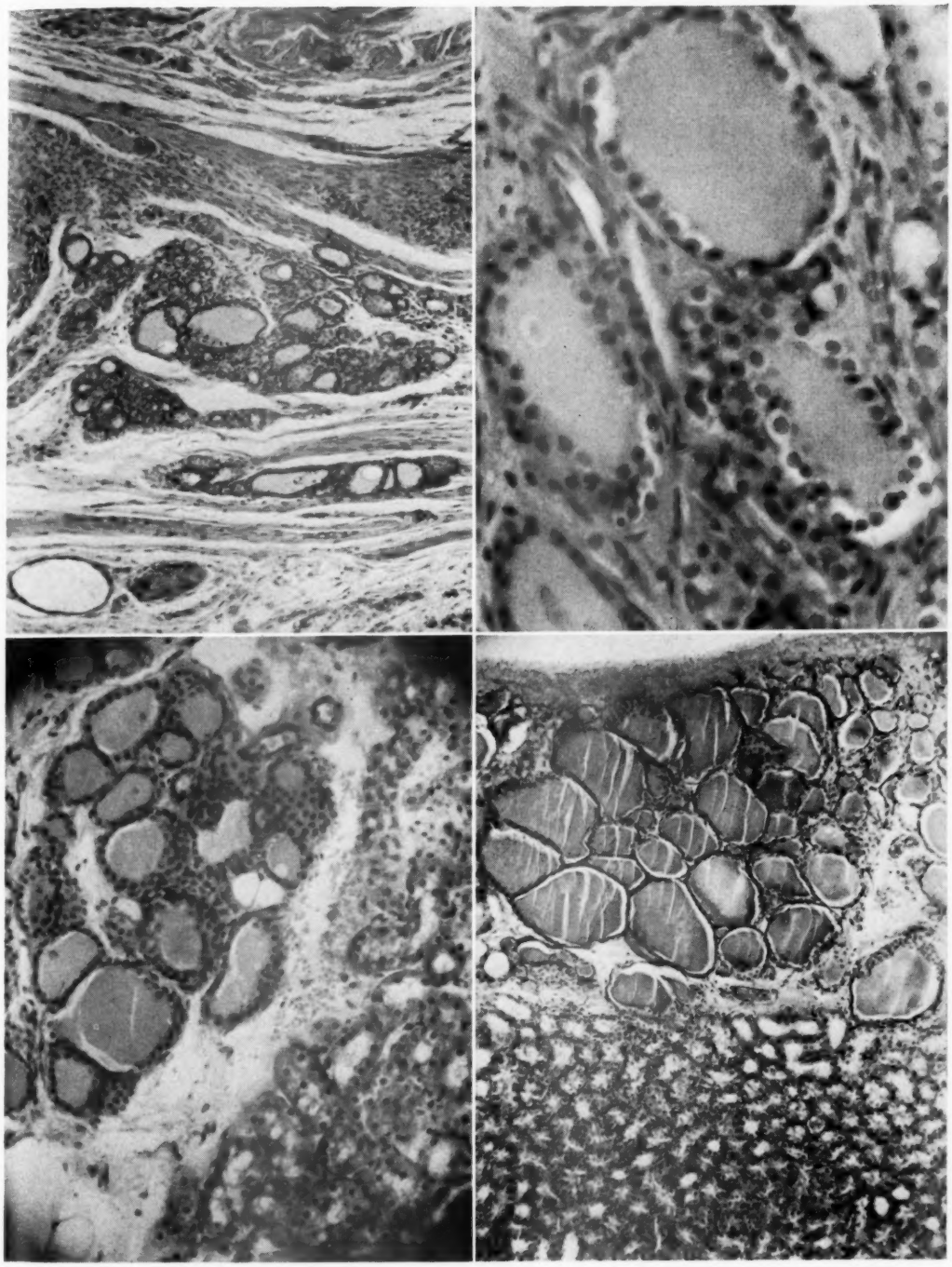

Fig. 3.

Fig. 4.

Fig. 1.—Animal No. A3. Autotransplant of thyroid to rectus sheath (×76, 1/11 off reduction).

Fig. 2.—Animal No. B1. Autotransplant of thyroid to renal capsule (×300, 1/11 off reduction).

Fig. 3.—Animal No. B3. Autotransplant of thyroid to renal capsule (×160, 1/11 off reduction).

Fig. 4.—Animal No. B4. Autotransplant of thyroid to renal capsule (×70, 1/11 off reduction).

Five of 6 hemithyroidectomized rabbits with autotransplantation of thyroid to serosa of stomach survived and all showed significant uptake of I^{131} (7,500 to 34,000 μc per minute). Three of five rabbits with transplantation to

Fig. 5.

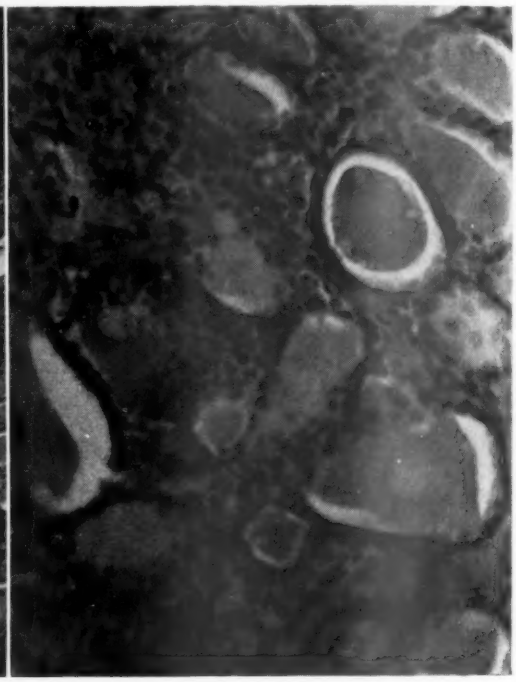

Fig. 6.

Fig. 5.—Animal No. C2. Autotransplant of thyroid to subserosa of the stomach (×64, 1/11 off reduction).

Fig. 6.—Animal No. C5. Autotransplant of thyroid to subserosa of the stomach (×200, 1/11 off reduction).

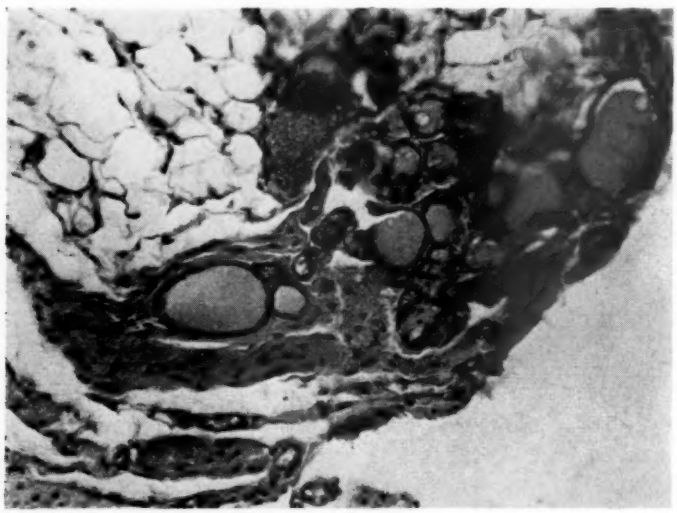

Fig. 7.—Animal No. D1. Autotransplant of thyroid to subcutaneous tissue (×156, 1/11 off reduction).

rectus sheath after total thyroidectomies survived. Two died of tetany. Both rabbits with hemithyroidectomies survived. All five showed good uptake of I^{131} (2,800 to 40,100 μc per minute).

Histologic examination was carried out on all of the specimens. Random sections were taken through the blocks of tissue. On microscopic examination, viable thyroid tissue composed of varying sized follicles, many of which contained colloid, was seen in all 5 transplants to the renal capsule, 2 of the 5 to the rectus sheath, and 4 of 5 to the stomach. It was also present in the areolar tissue near the iliac crest of the one rabbit in which a transplant was attempted to the bone marrow (Figs. 1-7). Since good uptake of I^{131} was demonstrated in all of the survivors, it was felt that serial sections through the blocks would demonstrate viable thyroid in the remaining specimens. More marked proliferation of thyroid follicles was seen in specimens transplanted beneath the renal capsule and in the subserosa of the stomach than in those placed within the rectus sheath.

Thus, in every rabbit surviving for one month after operation, there was significant uptake of I^{131}. This was observed whether the autotransplantation had been to the rectus sheath, the serosa of the stomach, or the kidney and whether a total thyroidectomy or hemithyroidectomy had been performed.

The almost uniform survival and function of the autotransplanted fragments of thyroid gland regardless of the site of transplantation would seem to indicate that the transplantation site is of only secondary consideration in the transplantation of tissue. There is, of course, a certain minimum amount of revascularization required for survival. In general, little blame for transplant rejection can be placed on the locality of the graft. Most of the failures in homotransplantation appear to be due, rather, to another factor, immunologic incompatibility. The results would seem to indicate that glandular deficiency

TABLE II. RESULTS OF AUTOTRANSPLANTATION OF THYROID GLANDS IN SURVIVING RABBITS

RABBIT NO.	AMOUNT THYROID REMOVED	UPTAKE	PATHOLOGY
Rectus sheath			
A1	Hemithyroidectomy	Good	Thyroid not seen
A2	Hemithyroidectomy	Good	Thyroid not seen
A3	Total thyroidectomy	Good	Viable thyroid
A4	Total thyroidectomy	Good	Thyroid not seen
A5	Total thyroidectomy	Good	Viable thyroid
Kidney			
B1	Total thyroidectomy	Good	Viable thyroid
B2	Hemithyroidectomy	Good	Viable thyroid
B3	Hemithyroidectomy	Good	Viable thyroid
B4	Hemithyroidectomy	Good	Viable thyroid
B5	Subtotal bilateral	Good	Viable thyroid
Stomach			
C1	Hemithyroidectomy	Good	Thyroid not seen
C2	Hemithyroidectomy	Good	Viable thyroid
C3	Hemithyroidectomy	Good	Viable thyroid
C4	Hemithyroidectomy	Good	Viable thyroid
C5	Hemithyroidectomy	Good	Viable thyroid
Subcutaneous tissue			
D1	Hemithyroidectomy	Slight	Viable thyroid

and therefore physiologic need played no detectable role in the successful outcome of thyroid autotransplants. It is likely that they play little role in the outcome of glandular homotransplants. This outcome seems to be determined by the same immunologic principles which govern grafting of any other tissue.

SUMMARY

1. In this study autografts of rabbit thyroid were transplanted to various sites in order to determine the effect of this factor on the grafting of tissue. In 4 of the surviving rabbits in the series, a total thyroidectomy was performed before transplantation was carried out.

2. The site of transplantation of thyroid gland was not found to be of primary importance in tissue survival. Good take and function of thyroid autografts were demonstrated whether transplantation was made to the renal capsule, subserosa of the stomach, or rectus sheath.

3. It was found that a physiologic glandular deficiency was not necessary to establish autograft survival. There was no significant difference between the survival of the grafted thyroid in animals having deficiency and in those with an adequate amount of residual gland left in situ.

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RECURRENT LARYNGEAL NERVE LESIONS DURING THYROIDECTOMY

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INTRODUCTION

IT HAS been my impression that by no means all recurrent laryngeal nerve lesions following thyroidectomy are actually due to damage inflicted upon the nerve at the time of operation. The school of thought, originated by Lahey, suggests that, if the nerve is dissected out at operation, it will not be divided, caught in a ligature or suture, or crushed by a forceps and so there is virtually no danger of a nerve lesion. This appears to be an oversimplification of the problem, since there is a possibility that the nerve may be damaged by post-operative changes in the wound, such as edema or pressure from blood clot. Previous experience[6] suggests that this is not too uncommon. An attempt has been made here to estimate the likelihood of a nerve lesion from such a cause.

METHOD OF STUDY

One hundred personal thyroidectomies for benign, nonrecurrent goiters have been investigated. Malignant and recurrent cases were excluded to make the series as uniform as possible. The qualification for inclusion in the series was that the patient should have had the larynx examined before, at the conclusion of, and a few days after operation. The most difficult examination was at the end of the operation. This could not be done in a number of patients who, therefore, had to be excluded. The chief aim of the investigation was to discover the number of patients who developed a vocal cord lesion in the days immediately after operation.

Before operation, the larynx was examined by indirect laryngoscopy by a laryngologist and in none of the 100 cases was a nerve lesion found.

OPERATION

All the operations were performed under a general anesthetic given through an endotracheal tube. The pretracheal muscles were split in the midline, except in a few cases in which the goiter was large; the muscles in these were divided transversely. The inferior thyroid artery was tied as often as possible and on only 11 occasions could it not be found. No attempt was made to isolate the recurrent nerve. A drain was used only on rare occasions. At the end of the operation, with the aid of the anesthetist, we examined the larynx by direct laryngoscopy and observed cord movements. At this stage, no patient was considered to have suffered a nerve lesion. Finally, 4 or 5 days later, the

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cords were examined by indirect laryngoscopy by a laryngologist. It was then found that 7 patients had a paralysis of one cord. These 7 patients were examined again at intervals and, in 5 cases, the nerve lesion made a full recovery. In 4 of these, recovery had occurred within 3 months but, in the other, it did not occur until 10 months had elapsed since the operation. Thus, of the 100 patients, 2 were left with a permanent nerve lesion.

If an inadequate resection of the thyroid is done, the risk to the nerve is greatly diminished, so the following figures are given. One patient developed transient tetany and 2 required some thyroid extract after operation. No patient has shown any sign of recurrent thyrotoxicosis. The first operation in the series was performed 6 years ago and the last, one year ago. One patient had to have a recurrent nodule near the region of the right upper pole removed 2 years after the original operation.

DISCUSSION

Of the 7 patients who developed a recurrent nerve lesion, all had actively moving cords at the end of the operation. Examination with a laryngoscope while the patient is still anesthetized is not as satisfactory as indirect laryngoscopy in the conscious patient, and the amount of cord movement varied a great deal in different individuals, depending mainly upon the depth of anesthesia. It is possible that a laryngoscope might impede cord movements, but it would not make a paralyzed cord move rhythmically during respiration. It was fortunate that, in patients who a few days later showed evidence of a nerve lesion, the cords were moving vigorously at the end of operation and left no doubt that the recurrent nerve had not suffered any injury during surgery. It can therefore be said with confidence that in none of these 7 patients was the recurrent nerve divided, since this would lead to an immediate cord paralysis. If the nerve had been crushed by a forceps or caught in a ligature or suture, one would suppose that it would have ceased conduction at least by the end of the operation. Stretching a nerve to produce a lesion has to be severe and prolonged.[1] If stretching of a nerve did occur in this series, it was certainly not prolonged and it is hoped that it was not severe. If any case of stretching, sufficient to cause nerve damage had occurred, impairment of nerve conduction should be evident by the end of the operation. The conclusion, therefore, seems to be that the damage to the nerve occurred after the operation.

POSSIBLE CAUSES OF POSTOPERATIVE LESIONS

There are several factors which have to be considered as possible causes of the lesion to the nerve following operation.

1. Blood Clot.—Blood clot in the wound is unlikely to cause pressure of any importance on the nerves, as has been previously observed.[6] Blood clot is too soft to be likely to cause pressure on the nerve and, if a tense clot formed beneath the pretracheal muscles, it would lead to serious interference with respiration. In this series, not one case showed any sign of a hematoma as deep as the muscles, though a small number required aspiration of blood from under the skin flap. None of the 7 cases was in this category.

2. Anemia.—The lesion is not likely to be due to anemia of the nerve, since it was not dissected out, so there should be no gross interference with its blood supply.

3. Fibrosis.—Fibrosis around the nerve can be firmly rejected as the cause, for it could not conceivably give rise to the nerve lesion 4 or 5 days after operation.

4. Edema.—The other explanation, and the one which seems to be the most convincing, is edema of the nerve, causing compression of its fibers. Mobilization of the lateral lobe of the gland and isolation of the inferior thyroid artery involves trauma which will be followed by edema. This dissection is in the neighborhood of the recurrent nerve, which may be involved in the edema. This risk would appear to be greater if the nerve itself is isolated.

RATE OF RECOVERY OF THE NERVE LESION

The nerve lesions in the 7 patients involved were noted on the fourth or fifth day after operation. They were examined periodically afterward and 4 had made a complete recovery within 3 months. The fifth, who recovered, first showed signs of recovery after 6 months and this was complete by the end of 10 months.

This rapid rate of recovery is further evidence that the nerve was not divided, crushed, or included in a ligature during the operation. If such an accident had happened, it is most unlikely that any recovery at all would have occurred.[1] Judd, New and Mann,[1] using dogs, found no recovery within one year following division, crushing, or ligature of a recurrent nerve.

THE PROBLEM OF NERVE DISSECTION

The chief argument relating to the recurrent nerve in thyroid surgery is whether or not it should be exposed at operation. The answer can only be given by finding which method supplies the better results, but most of the figures available cannot be interpreted accurately. Lahey and Hoover[3] claimed that the incidence of nerve lesions had been reduced from 1.6 to 0.3 per cent by routine exposure of the nerves. Unfortunately, the larynx was not examined in every case after operation. Even if the nerves are seen to be intact at the end of the operation, it cannot be assumed, as done by Lahey,[2] that cord function will be normal as already indicated above. Wade[5] reported no lesions after exposure of the nerves in 84 cases, all of which were examined laryngologically. As most of these were examined several months after operation, it is possible that transient paralyses occurred even in this group. Piercy[4] reported 0.4 per cent permanent cases of nerve injury without exposure of the nerve but apparently does not make a routine laryngologic examination.

It is impossible, I am sure, to say with certainty whether or not a patient has a paralyzed cord during the postoperative period, except by inspecting the larynx. The voice is an unreliable guide. It may be impaired for a few days from the pressure of the endotracheal tube during operation or by postoperative discomfort and give a misleading impression of nerve damage. On the other

hand, the voice may seem normal though one cord is immobile. Respiration also was not found to be a reliable guide at this stage. In fact, it was not possible to predict the laryngologic findings with complete accuracy. On several occasions, it was felt that a cord lesion was probable but none was found, and the contrary occured as well. It is strongly believed that reports of nerve lesions after thyroidectomy which are not based upon laryngologic examination of all patients are of dubious value.

In this series, the nerve was never deliberately exposed and it was remarkable how rarely it was seen. In all cases, a search was made for the inferior thyroid artery. The vessel was cleared and tied well away from the gland under direct vision so that there was no possibility of the nerve being included in the ligature. Before resection was begun, the surface of the gland was carefully examined to make sure that the nerve was not adherent to it. As emphasized by the supporters of exposure, the nerve is reasonably large and easy to see. This being so, if it is in the surface of the gland, it should be seen before it can be damaged. It does not run through gland tissue,[7] though it may be apparently buried by a nodule of gland. But again inspection should insure that the nerve is not included in the line of resection.

Certain objections can be brought against the policy of exposure of the recurrent nerve. In the great majority of cases, it divides into 2 terminal branches at varying distances up to one inch from the larynx. If only one of these divisions is found, the other may still be damaged. So logically both of these branches should be isolated. Exposure of the nerve is bound to cause trauma in its neighborhood and will be followed by varying degrees of edema, which may lead to a nerve lesion, though probably of a temporary nature. This would occur without any visible damage to the nerve during operation. Bleeding during the dissection is a hazard which may lead to direct nerve damage during hemostasis.

It is usually considered that the nerve is most liable to be damaged close to the larynx, since it is here most closely related to the gland. Wade[5] concluded that the nerve is only slightly more vulnerable in its upper third than in its middle or lower thirds. Lahey and Hoover,[3] however, found that, in practically all cases with a lesion which they explored, the nerve had been injured near the larynx. This certainly is the region where the nerve is anatomically closest to the gland and where the greatest care should be exercised.

SUMMARY

1. One hundred cases of thyroidectomy have been studied for recurrent laryngeal nerve lesions.

2. No cases appeared to have had any nerve damage by the end of the operation, but 7 were found to have a unilateral lesion during the few days after operation. Of these, 5 recovered and 2 had a permanent lesion.

3. It is suggested that the cause of the postoperative lesion is edema near the nerve, causing compression of its fibers.

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OBSERVATIONS CONCERNING THE PERITONEAL FLUID IN EXPERIMENTAL STRANGULATED INTESTINAL OBSTRUCTION: THE EFFECTS OF REMOVAL FROM THE PERITONEAL CAVITY

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SINCE the turn of the century, there has been a sustained decrease in the mortality rate of intestinal obstruction.[3] Factors contributing to the improvement in the prognosis of this condition include judicious replacement of water and electrolyte losses, effective decompression of the intestine through the use of indwelling tubes, adequate replacement where blood loss is a factor, and early operation in cases of irreversible obstruction. The usefulness of antibiotics has also been established in view of the significant role played by bacteria in the pathogenesis of irreversible changes in the bowel wall.[2]

Although there has been improvement in the survival rates of all patients presenting with obstruction, the most striking advances have been made in the treatment of simple obstruction. Strangulated obstruction still yields mortality rates suggesting the importance of other factors against which our therapeutic armamentarium is not yet effective.

It is well established that the peritoneal cavity of experimental animals dying of strangulated intestinal obstruction is the site of collection of large amounts of dark, foul fluid. There is evidence to indicate that this material is toxic and does play an important role in the death of these animals.[4] The purpose of this study was to determine (1) whether or not this fluid was lethal when injected into the peritoneal cavity of normal dogs, (2) the length of life following injection of a lethal dose into the peritoneal cavity, (3) the effect of aspirating the material after a standard period of time, and (4) the effect of aspiration of the fluid combined with copious irrigation of the peritoneal cavity after the same length of time.

MATERIALS AND METHODS

All Animals.—Fifty-four unselected mongrel dogs were used in these experiments. Sterile technique was utilized in carrying out all operative procedures. Anesthesia was induced and maintained by fractional intravenous doses of Nembutal. Food and water were withheld on the day of operation but offered to all animals during the postoperative period. No supportive measures or antibiotics were used during the pre- or postoperative periods.

Donor Animals.—In order to measure the effects of peritoneal fluid, it was elected to inject fluid from the peritoneal cavity of dogs dying from strangulated obstruction directly into the peritoneal cavity of normal animals. This would eliminate factors such as loss of blood, fluid, and electrolytes, as

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well as other alterations engendered by strangulated obstruction. Accordingly, the venous supply of a segment of ileum 15 cm. in length was divided and ligated. The marginal vessels were also ligated at the distal extremities of this segment. Closed loop obstruction was then produced by an encircling tie of umbilical tape (Fig. 1). At or shortly before death, the peritoneal cavity was opened and the accumulated fluid removed. Six large animals served as fluid donors.

Control Animals.—Initially, the injection of fluid into the peritoneal cavity of control dogs was carried out without the benefit of anesthesia. It soon became apparent that this was very painful, and, therefore, these animals were also anesthetized. In order to arrive at a small lethal dose, animals were injected intraperitoneally with amounts ranging from 0.1 to 18 c.c. per kilogram of body weight. The selected dose was injected into the peritoneal cavity, following which the animals were returned to their cages.

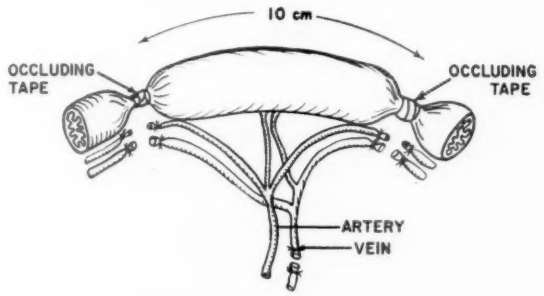

Fig. 1.—Diagram illustrating method of producing strangulated obstruction.

Treated Animals.—These animals were divided into 2 groups. Three cubic centimeters of fluid per kilogram of body weight was injected into the peritoneal cavity of each animal comprising the first group. After an interval of 5 minutes, the peritoneal cavity was opened through a midline incision, and thorough suction of the free fluid was carried out. This maneuver was greatly facilitated by withdrawal of the intestines from the abdomen. After replacement of the viscera, the abdomen was closed in layers. The animals were returned to their cages for observation.

The second group of animals was treated in a similar manner, with the addition of thorough irrigation of the intestines and the peritoneal cavity with one liter of saline or Ringer's solution.

RESULTS

The donor animals recovered rapidly from anesthesia, moved about their cages actively, and appeared to be normal for about 24 hours. After this period they became less active, pursuing a rapid downhill course for the next 5 to 8 hours. Just before death, the respiratory rate, pulse rate, and temperature all became elevated. Depending upon the size of the dog, from 300 to 500 c.c. of dark, foul peritoneal fluid was withdrawn. The strangulated segment was found collapsed, although no area of gross perforation was seen. The surfaces of the other abdominal viscera were red and inflamed in appearance. The intestines were of small caliber with thick walls.

In the control group, it appeared that 3 c.c. per kilogram was an appropriate small lethal dose (Table I). A total of 8 animals received this amount with no 25-hour survivors (Table II). There appeared to be no correlation between the time of refrigeration of the fluid and the lethal effect. The average survival time was 12.2 hours with extremes of 6 and 24 hours. After recovery from anesthesia, these animals appeared lethargic until the time of death. They refused water and food, behaving in a somewhat similar manner to the donor dogs just before death.

TABLE I. LETHAL EFFECTS OF VARIOUS DOSES OF PERITONEAL FLUID

NUMBER OF DOGS	AMOUNT GIVEN (C.C./KG.)	NUMBER OF 25-HOUR SURVIVORS
2	0.1	2
2	0.5	2
3	1.0	3
1	2.0	0
8	3.0	0
2	10.0	0
1	15.0	0
1	18.0	0

TABLE II. RESULTS IN DOGS GIVEN PERITONEAL FLUID (3 C.C./KG.) WITHOUT ATTEMPTS AT REMOVAL

DOG NUMBER	AMOUNT GIVEN (C.C.)	SOURCE—DONOR DOG NUMBER		TIME FLUID REFRIGERATED (HOURS)	SURVIVAL TIME (HOURS)
197	15	31	98	2	6
12	21	31	98	14	7
19	16	31	98	14	12
194	20	19	196	4	24
75	25	19	196	24	10
18	24	63	95	28	18
21	23	63	95	24	12
38	28	63	95	4	9

Ten animals in which the fluid was aspirated from the peritoneal cavity after a 5-minute interval had an average survival time of 12.7 hours (Table III). The extremes for this group were 3 and 26 hours. Their course after operation was very similar to control animals receiving the same dosage.

TABLE III. RESULTS IN DOGS GIVEN PERITONEAL FLUID (3 C.C./KG.) WITH ASPIRATION FROM THE PERITONEAL CAVITY AFTER FIVE MINUTES

DOG NUMBER	AMOUNT GIVEN (C.C.)	SOURCE—DONOR DOG NUMBER		TIME FLUID REFRIGERATED (HOURS)	SURVIVAL TIME (HOURS)
7	18	19	196	2	10
52	24	19	196	2	13
29	21	19	196	14	13
174	18	63	95	14	3
192	18	63	95	14	14
199	18	63	95	14	12
28	28	63	95	26	26
23	30	63	95	26	14
190	23	63	95	26	6
182	21	63	95	26	16

Animals in which thorough lavage of the peritoneal cavity was effected after aspiration of the fluid survived much longer than the preceding groups.

Observations were terminated at the end of one week, although 4 animals lived indefinitely. Post-mortem examination of the 80-, 95-, and 96-hour survivors revealed diffuse peritonitis with multiple abscesses. The average survival time for this group was 108 hours (Table IV). Five-day survivors became active, taking oral nourishment readily.

TABLE IV. RESULTS IN DOGS GIVEN PERITONEAL FLUID (3 C.C./KG.) IN WHICH THE PERITONEAL CAVITY WAS IRRIGATED WITH ONE LITER OF RINGER'S SOLUTION AFTER FIVE MINUTES

DOG NUMBER	AMOUNT GIVEN (C.C.)	SOURCE—DONOR DOG NUMBER		TIME FLUID REFRIGERATED (HOURS)	SURVIVAL TIME (HOURS)
177	25	31	98	2	96
105	22	31	98	2	45
154	24	31	98	14	168*
186	35	31	98	14	60
188	28	31	98	14	168*
161	23	31	98	14	32
45	24	19	196	14	168*
200	24	19	196	4	80
178	30	19	196	28	95
172	22	19	196	28	168*

*Observation discontinued after one week.

DISCUSSION

Death from obstruction of the small intestines may result from a number of factors. Rapid loss of fluid and electrolytes may be fatal factors in death resulting from high intestinal obstruction. Where there is strangulation of a long segment of intestine, blood loss may be sufficient to precipitate irreversible shock. Perforation of a short obstructed segment may occur with generalized peritonitis. Intestinal distention for long periods may have a detrimental effect upon the balance between various physiologic processes. The mechanism of death in closed loop strangulation of relatively short segments of bowel differs from those mentioned above. Under these circumstances, anaerobic organisms proliferate rapidly. Toxins begin to accumulate, among which is hyaluronidase, a highly potent spreading factor which hastens the permeability of the ischemic bowel wall.[5, 6] With loss of the integrity of bowel wall components, contents of the obstructed segment rapidly gain access to the peritoneal cavity. Among the toxins which are readily absorbed at this stage are lecithinase and fibrinolysins. The former is the highly lethal alpha toxin produced by *Clostridium welchii,* while the latter negates localization by lysis of fibrinous adhesions. It appears that breakdown products of hemoglobin are not primary lethal agents.[1]

The lethal effect of unaltered peritoneal fluid recovered late in the course of strangulated obstruction in the dog was consistently demonstrated. The time of death in donor animals correlated well with the appearance of this dark, foul fluid. Each animal produced enough fluid to kill 7 animals of the same weight. Results of this study indicate that aspiration of the fluid 5 minutes after injection into the peritoneal cavity of normal dogs failed to improve survival time over the control animals. Inspection revealed a thin layer of the material which remained over the surface of the intestine after aspiration.

Irrigation fluid, returned from the peritoneal cavity and intestinal surface, was dark brown initially, becoming lighter with successive washings. That bacteria would cause death so rapidly is not probable, although post-mortem examination of irrigated animals dying after several days gave evidence of a bacterial peritonitis. That early death as seen in animals not receiving irrigation resulted from toxins already present in the fluid certainly must be strongly considered. Irrigation of the peritoneal cavity could be expected to remove and dilute the toxins to a degree so as to obviate a fatal outcome, thereby accounting for the prolonged survival time in this group (Fig. 2).

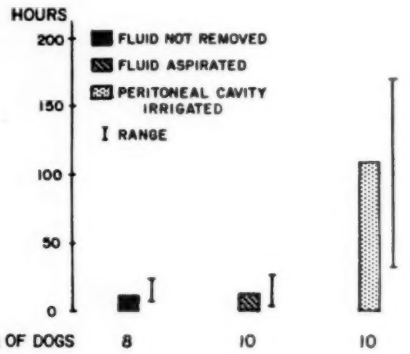

Fig. 2.—Comparison of survival time in the 3 groups.

CONCLUSIONS

1. Peritoneal fluid occurring late in the course of strangulated intestinal obstruction in dogs is lethal when amounts as low as 3 c.c. per kilogram are injected into the peritoneal cavity of normal dogs.

2. The average survival time in animals receiving this dosage was 12.2 hours.

3. The survival time was not extended by aspiration of the fluid after a 5-minute interval.

4. Animals receiving thorough irrigation in addition to aspiration of the fluid after a 5-minute interval had an average survival time of 108 hours. This includes observation time of one week for 4 animals recovering completely.

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DANGER OF INTRAPERITONEAL NEOMYCIN DURING ETHER ANESTHESIA

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NEOMYCIN has been implicated as the causative agent in 4 cases of respiratory arrest, including 2 deaths, reported by Pridgen[3] and in a fifth case of respiratory arrest with eventual recovery which recently occurred in our hospital. Another instance of apnea with possible neomycin implication has been reported.[1] The fact that apnea occurred shortly after intraperitoneal administration of neomycin to surgical patients anesthetized with ether suggested a causal rather than coincidental relationship between the antibiotic and this anesthetic agent. Poth[2] did not state the anesthetic agent employed in his case of serious respiratory depression after intraperitoneal neomycin. A study was undertaken to determine the neuromuscular blocking action of neomycin, the potentiation of this effect by ether and its antagonism by neostigmine. The results of this pharmacologic study are summarized below; a detailed account will be published elsewhere.

In a series of 13 rabbits using a sciatic nerve–gastrocnemius muscle preparation, intravenous neomycin was readily capable of producing neuromuscular blockade to indirect nerve stimulation. In rabbits anesthetized with ether complete neuromuscular blockade could be produced, in some instances, with intravenous doses as low as 2 mg. per kilogram. Unanesthetized rabbits required 10 to 20 times the above dose to produce similar responses. This clearly illustrates the potentiating effect of ether on the neuromuscular blockade produced by neomycin.

In dogs anesthetized with ether, intravenous neomycin (10 mg. per kilogram) produced nearly 100 per cent block of the sciatic-gastrocnemius preparation with simultaneous reduction in the respiratory minute volume to about 10 per cent of control values. Neostigmine antagonized the neuromuscular blockade as well as the respiratory depression in these animals.

Pretreatment of unanesthetized rabbits and mice with intravenous neostigmine was effective in protecting both species of animals from fatal doses of neomycin administered intravenously and intraperitoneally.

The above pharmacologic studies strongly suggest that the clinical reports of apnea following neomycin lavage of the peritoneal cavity during ether anesthesia was in all probability due to the neuromuscular blocking properties of neomycin potentiated by the anesthetic agent. It must be remembered that intraperitoneal injection of a compound is usually followed by rapid absorption of the agent into the systemic circulation.

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We feel that the intraperitoneal use of neomycin in a patient during ether anesthesia greatly increases the risk of severe respiratory depression. If the circumstances of peritoneal contamination seem to justify the concomitant use of these agents, especially close attention should be paid to the respiratory stat of the patient postoperatively. Since the neuromuscular blocking action ether is persistent after discontinuation of this anesthetic agent, intraperitonea administration of neomycin to a patient who had received ether earlier in the course of an operative procedure may still result in respiratory depression.

The effect of intraperitoneal administration of neomycin during anesthesia with agents other than ether has not been studied. However, since neomycin alone has been demonstrated in animals to cause neuromuscular blocking and respiratory depression leading to death, its administration by this route presents a potential danger which should be recognized.

The study suggests that neostigmine administered intravenously with caution may be beneficial as an adjunct to artificial ventilation in the treatment of respiratory depression caused by neomycin.

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PERINEAL HERNIA REPAIR WITH NYLON MESH

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THIS report is rendered with two purposes in view: (1) to discuss the nature of postexenteration perineal hernia and describe its repair and (2) to cite another circumstance in which nylon mesh has been successfully used in providing support to human tissue. So far, the literature contains only a few reports of nylon's use in the form of a coarse[6] and fine[1] mesh for repair of human abdominal wall hernias and in fine mesh form for repairing experimentally created defects in dogs.[2, 5]

Herniation through the perineum after pelvic exenteration for advanced pelvic cancer would, at first glance, seem almost inevitable. Included with the block of pelvic viscera resected are most of both levators, vagina, labia, anus with external sphincter, and the intervening perineal body (Fig. 1). Reconstruction consists simply in approximating the remaining skin along a line running fore and aft from pubic symphysis to coccyx, leaving an opening at the coccygeal end for drainage. Perineal healing is usually prompt.

Prolapse of small bowel and omentum into the denuded pelvic cavity occurs immediately. The degree of prolapse is determined by the length of the mesentery of the small intestine. In most instances it is not long enough to protrude through the perineal defect. Within a few weeks the walls and floor of the pelvis develop a lining of regenerated peritoneum into which the surfaces of prolapsed abdominal organs may become incorporated. Presumably because these surfaces are broad in the female pelvis, acute angulation and consequent obstruction of adherent small bowel rarely occurs.

When the patient resumes an active life, the weight of the abdominal viscera is directed outward and downward against the pelvic walls and perineum. Adhesion of small bowel to itself and to lateral pelvic wall plus upward pull by the small bowel mesentery and perhaps by the omentum counteract this downward thrust. In most instances such support and traction factors have been adequate to prevent significant herniation. In the occasional patient, however, these factors are deficient or become so with time. The perineal skin slowly sags under the weight. Ultimately the patient finds her activities increasingly restricted by a bulge which hangs between her legs when she stands and intrudes between her and the chair when she sits (Fig. 2).

Contrary to expectation, only 2 of the patients restored to useful lives by total pelvic exenteration for carcinoma of the cervix in the senior author's personal series have so far developed distressing perineal hernias.

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The first of these 2 patients presented herself for treatment in November, 1954. To correct her hernia, it was obviously necessary to construct across the pelvic outlet, above the perineal skin, a sling of living or inert material which would be strong enough to bear the downward thrust. This material had to be securely anchored to the bony pelvis and be so constituted that it would not stretch, disintegrate, slough, erode hollow viscera, or excite disruptible inflammatory reaction. The simplest solution seemed to be the use of a mesh of foreign material. Tantalum and nylon mesh both were available. The nylon was selected because, unlike tantalum, it would not fragment with the passage of time or present rough ridges or sharp wire ends to apposed bowel. Although tantalum has been better tolerated than plastic materials in the presence

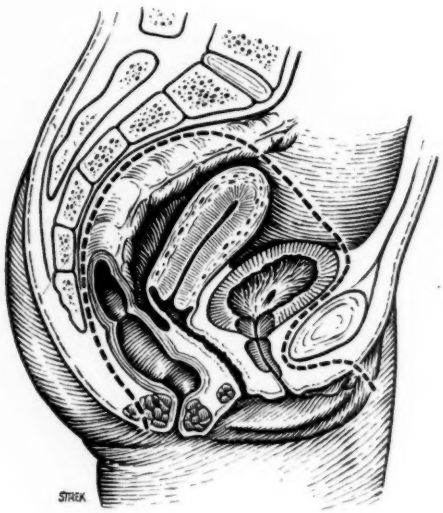

Fig. 1.

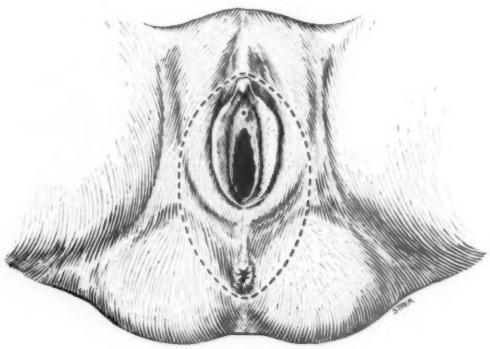

Fig. 2.

Fig. 1.—Viscera and perineal structures removed in total pelvic exenteration. Longitudinal cross section view.

Fig. 2.—Usual extent of perineal incision in pelvic exenteration operation.

of sepsis,[3, 4] such a complication was not considered likely. The perineum had been well healed for many months prior to the time of perineal reconstruction, and the urine and feces were being discharged from colostomies on the anterior abdominal wall, well away from the operative field.

The procedure devised for the second patient was basically the same except that loops of small bowel had to be dissected free from the perineal scar.

OPERATIVE PROCEDURE

A Miller-Abbott tube introduced well down into the small bowel prior to surgery is indispensable. This maneuver allows the small bowel to thread itself on the inlying tube, thereby tending to keep the redundant loops out of the pelvis. It also serves as a safety vent in the event that the small bowel is damaged in dissecting it free from the adherent scar.

With the patient in lithotomy position, the bulging perineum, thighs, lower abdomen, and distal buttocks are prepared and draped. The perineal skin

is incised from the mons to the coccyx (Fig. 3). A plane of dissection is created in the thinned out fibrous tissue between the skin and peritoneum and extended laterally in both directions until the periosteal surfaces of the descending pubic rami are exposed. As these surfaces are followed downward toward the ischium, the residua of levator fascia and muscle are encountered and developed posteriorly toward the coccyx. A double sheet of nylon mesh of suitable dimensions is selected. One corner is sutured to the ligamentous tissue at the coccyx. It is then anchored posterolaterally to the remnants of the levator ani muscle and fascia and anterolaterally to the inner periosteal surfaces of the pubic rami. Anteriorly, it is fixed to the pubic symphysis (Fig. 4), using No. 36 gauge monofilamentous stainless steel wire. The skin flaps are trimmed so that when approximated they lie as snugly as possible against the nylon's undersurface. Penrose drains are placed in the space between skin and mesh and brought out through the posterior end of the incision.

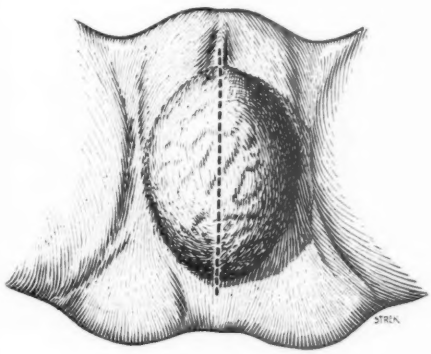

Fig. 3.

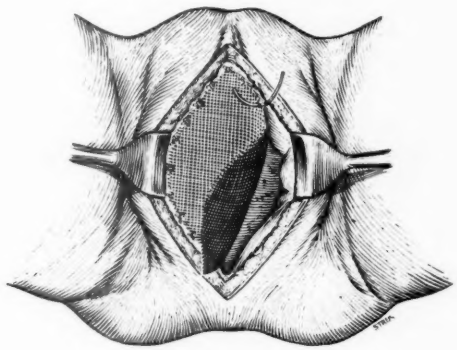

Fig. 4.

Fig. 3.—Hernial bulge, external view. Line of incision indicated by broken line.

Fig. 4.—Nylon sheet is being sutured in place across pelvic outlet. Skin margins have been trimmed of redundant tissues, will be subsequently drawn together in the midline over the nylon mesh.

Certain aspects of this procedure deserve more detailed discussion. Dissecting the skin flaps off the regenerated peritoneum is technically very difficult. The hernial wall proves at operation to consist of a thinned out fibrous residuum of the subcutaneous fat layer, covered outside by stretched skin and inside by mesothelium. Wherever small bowel has become adherent to the inner surface of perineal skin, peritoneum does not regenerate. Thus, the problem is to split the fibrous middle layer without buttonholing skin or peritoneum and without entering the lumen of an adherent small bowel loop. Should the small bowel lumen be opened by dissection it is wise to resect the entire adherent segment so that an accurate end-to-end anastomosis can be constructed with mobile ends whose muscular and peritoneal coats are intact and capable of holding sutures. If the peritoneal layer becomes torn or is deliberately incised to facilitate management of small bowel defects, closure is attempted. Gaps are accepted without concern, however, since peritoneum will regenerate over the exposed nylon mesh.

CASE REPORTS

CASE 1.—M. C., aged 54 years, a stocky and obese housewife, underwent total pelvic exenteration for Stage IV squamous carcinoma of the cervix in June, 1953. The ureters were transplanted into the sigmoid which was brought out through the abdominal wall in the left lower quadrant as an end colostomy. The transverse colon was brought out through the upper end of the incision over a rod as a loop colostomy to divert the fecal stream. Subsequently, the distal stoma of the transverse loop colostomy was closed to stop retrograde leakage of urine onto the upper abdominal wall. In this case, exenteration included total vulvectomy. A single long perineal defect resulted. At the close of the abdominal portion of the operation, she was placed in lithotomy position and the perineum closed around Penrose drains with interrupted 2-0 silk sutures. The drains were removed on the ninth postoperative day; the perineal sutures were removed on the fourteenth postoperative day. After a 70-day convalescence complicated by wound dehiscence, she returned to Maine wearing an ileostomy bag over the end sigmoid stoma. By the time she was discharged home, the perineum was solidly healed and did not bulge when she stood or walked.

She gradually resumed an active life. Perineal bulging became evident 6 months after the operation, associated with some perineal pain and pressure on walking. These symptoms increased until she demanded treatment.

The repair was done on Nov. 3, 1954, using a double layer of nylon mesh. Neither small bowel nor peritoneum was entered. Small strips of perineal skin were excised to effect snug application of skin to nylon mesh after skin closure. The potential space between mesh and skin was drained at the posterior angle of the closure line with a Penrose soft rubber tube, which fell out 5 days later. Drainage was minimal. Sutures were removed on the twelfth postoperative day, following which a regime of bidaily Sitz baths was begun. The drain site had filled in with clean granulations 3 days later and she was discharged (fifteenth postoperative day). Except for a transient rise in temperature to 100.5° F. on the second postoperative day, healing proceeded without either local or systemic evidence of inflammation.

At her latest follow-up visit in September, 1956, her general health was excellent. For the past several months she had been doing all the cooking and housework for her large household. The perineum was solidly healed, pliant but without any bulging, the skin smooth and healthy. A small umbilication was still present at the old drain site which occasionally produced a drop of serosanguineous drainage from small granulations at its core. She was entirely satisfied with the result.

CASE 2.—M. W., a 49-year-old clerical worker, developed a perineal hernia 18 months following total pelvic exenteration for Stage IV squamous carcinoma of the cervix. A dome-shaped perineal bulge, roughly 15 by 20 cm. in size, was present when she stood. It interfered greatly with walking and she had to perch on the edge of the chair to avoid sitting on the mass.

Her operation was performed on May 20, 1955. With the patient in the lithotomy position, the hernial sac was dissected. A loop of bowel was found to be adherent to the regenerated peritoneal lining of the sac. In attempting to free the bowel the lumen was entered. The redundant bowel presented in the perineal wound. It was resected and end-to-end anastomosis carried out. The peritoneal layer was closed with a continuous catgut suture. A double sheet of nylon mesh was sutured in place, redundant skin excised, and perineum closed over a drain. The drainage became profuse and purulent, culturing out a mixed flora of intestinal tract organisms. This superficial sepsis was treated with frequent hydrogen peroxide-saline irrigations and later Sitz baths. Invasive sepsis did not supervene. By the twelfth day drainage had ceased and firm healing resulted without trapped fluid collection.

Now, 23 months since the repair, there is no recurrence. The perineum is smooth and somewhat rounded without any sagging in the erect position. There are no draining sinuses or unhealed granulations. She, too, is entirely satisfied with the result.

SUMMARY

Perineal hernia, a late sequel to pelvic exenteration, has been discussed and the technique of its operative repair in 2 patients described.

In these 2 cases, a double-layered nylon mesh has proved a safe and satisfactory substitute for the surgically absent supporting muscles and fascia of perineum and pelvic floor.

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CHOLECYSTECTOMY AND CHOLANGIOGRAPHY

A Study of 274 Cases

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FROM July 1, 1954, to March 1, 1957, 274 cholecystectomies were performed at the Robert B. Green Memorial Hospital for cholecystitis and cholelithiasis. A routine operative cholangiogram was performed on 172 of these cases. All of the cholecystectomies and cholangiograms were done by first, second, and third year general surgery residents. This paper is a study of these cholecystectomies plus a critical evaluation of the results of the operative cholangiograms performed.

Table I shows the age distribution of the patients. The range was 17 years to 85 years with an over-all average of 42 years. Of the total number of cases, 86 per cent were Latin American women. There were no Negro men in the entire series.

Table I. The Number of Persons in Each Age Group Undergoing Surgery

AGE (YEARS)	15-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	TOTAL
Women	5	49	76	43	27	24	7	1	232
Men	2	4	2	7	10	8	7	2	42
Total	7	53	78	50	37	32	14	3	274

On admission to the hospital 30 cases gave a history of jaundice and examination revealed a palpable mass in the right upper quadrant of the abdomen in 41 cases.

A preoperative oral cholecystogram was done on 221 of the cases. There was function without calculi in 8, function with calculi in 90, calculi with no function in 33, and neither function nor calculi in 80 cases.

Surgery was performed as an emergency procedure in 20 cases and as an elective procedure in 254 cases. At surgery the surgeon reported finding 236 gall bladders containing palpable calculi. However, on pathologic examination, 262 of the gall bladders were reported to contain calculi. Forty-five cases were found to have a dilated common bile duct and 21 palpable common duct calculi were noted.

There were 84 common bile-duct explorations which revealed pathology in 45 cases (53 per cent). Table II is a summary of the reasons for common duct exploration as reported by the surgeon.

Photographs in this paper were made of actual cholangiograms that were considered satisfactory by the surgeon who performed them. These errors are the most common which were found in this series of cases.

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TABLE II. REASONS FOR AND RESULTS OF COMMON DUCT EXPLORATION

	REASON	NUMBER	STONES PRESENT	PERCENTAGE CORRECT
I.	Common duct dilated (alone)	17	7	41
	a. Plus a palpable common duct calculus	18	17	95
	b. Plus a history of jaundice	8	4	50
	c. Plus a suspicious cholangiogram	6	2	33
II.	Common duct calculus palpated (alone)	5	5	100
	a. Plus a history of jaundice	5	5	100
	b. Plus a suspicious cholangiogram	2	2	100
III.	Suspicious cholangiogram (alone)	8	2	25
IV.	Others	9	0	0
V.	Reason not given	6	1	16
	Total	84	45	53

The anesthetic record on each of the patients was carefully examined in this study and the operating time from the skin incision to complete closure was recorded. Table III shows the results of this analysis with a distribution of the times as they are related to the various operative procedures. This shows a difference in the average operative time of 41 minutes between cholecystectomy alone and cholecystectomy plus routine operative cholangiography. It will be noted that when an appendectomy was done with the cholangiogram the average time for the procedure was prolonged by 44 minutes. This is accounted for by the fact that the appendectomy usually was done while the surgeon was waiting for the return of the cholangiogram from the darkroom.

TABLE III. TIME REQUIRED FOR THE VARIOUS OPERATIVE PROCEDURES

	TYPE PROCEDURE	TIME GROUPS IN MINUTES					TOTAL NO.	TIME (MINUTES)	
		0-59	60-119	120-179	180-239	240-299		AVE.	MED.
I.	Cholecystectomy (alone)	1	20	15	2	0	38	113*	105
II.	Cholecystectomy (alone) plus appendectomy	0	9	9	2	0	20	122*	120
III.	Cholecystectomy (with and without) appendectomy	1	29	24	4	0	58	116	115
IV.	Cholecystectomy (alone) plus cholangiogram	0	16	24	20	3	63	154*	150
V.	Cholecystectomy (with and without) appendectomy plus cholangiogram	1	31	55	38	5	130	157	150

*Standard deviation for I = 21.6, II = 38.8, and IV = 45 minutes respectively.

The standard deviations for 3 of the groups of the series are in the foot note of Table III. From these values a determination of the statistical signifi cance of these figures can be made from the following formula:

$$\sigma = \sqrt{\frac{(d_1)^2}{N_1} + \frac{(d_2)^2}{N_2}}$$

where σ = the standard error of the difference between two means,
d_1 = the standard deviation of the first group,
d_2 = the standard deviation of the second group,
N_1 = the number of cases in the first group, and
N_2 = the number of cases in the second group.

If values from Table III, Groups I and IV, are used the standard error of the difference of 2 means is equal to 6.9 minutes, with an actual difference of the means of 41 minutes. This gives a ratio of 6 to 1. Arkin and Colton[1] state that the odds against this difference happening by chance sampling are 500 million to one.

The major complications of the postoperative period are listed in Table IV. It is interesting that there were recorded 8 cases of residual common duct stone on follow-up T-tube cholangiogram. Two cases were reoperated upon and explored. A stone was found in one case and no stone in the other. In one of the 8, the T-tube was removed about 3 weeks postoperatively, in spite of the positive cholangiograms, and the patient died shortly thereafter from an acute pancreatitis. The residual stone and pancreatitis were confirmed at autopsy. The 5 remaining cases were not reoperated upon and the stones, if present, apparently passed into the duodenum as they were not seen on subsequent T-tube cholangiograms. In one case an incidental appendectomy was done with elective cholecystectomy. The patient developed a typical mechanical obstruction and re-exploration was done on the seventh postoperative day. A loop of ileum was found bound down to the site where the appendix had been removed causing a complete mechanical obstruction.

TABLE IV. MAJOR POSTOPERATIVE COMPLICATIONS

TYPE	NUMBER
Wound infections	29
Residual common duct stones	8
Hematoma of wound	4
Subphrenic abscess	3
Deaths	3
Abortions within one week postoperatively	2
Subhepatic abscess	1
Evisceration	1
Total	51

Table IV shows the relationship between the wound infection rate and the various operative procedures. No stitch abscesses are included in this analysis. It appears that the wound infection rate increased as the number of operative procedures performed increased. This was not accounted for completely by the increase in operating time. Of the 57 cases which had no cholangiogram or common duct exploration there were only 2 wound infections producing a rate

of 3.0 per cent. In the 129 cases in which a cholangiogram was made but the common duct was not explored there were 13 wound infections or a rate of 10.0 per cent. The difference in rates, 7 per cent, is statistically significant.

TABLE V. RELATIONSHIP BETWEEN THE TYPE OF OPERATIVE PROCEDURE PERFORMED AND THE WOUND INFECTION RATE

	TYPE PROCEDURE	NUMBER	INFECTIONS	PERCENTAGE
I.	Cholecystectomy	37	0	0
II.	Cholecystectomy plus cholangiogram	62	4	6.5
III.	Cholecystectomy plus appendectomy	20	2	10.0
IV.	Cholecystectomy plus appendectomy plus cholangiogram	67	9	13.4
V.	Cholecystectomy plus common duct exploration	51	8	15.7
VI.	Cholecystectomy plus appendectomy plus common duct exploration	35	6	17.7
	Total	272	29	10.6

CHOLANGIOGRAPHY

During the latter half of the period which this study covers, a routine operative cholangiogram was done on almost all of the patients undergoing surgery for cholecystectomy. A total of 168 routine operative cholangiograms were done in this period, not including operative T-tube cholangiograms.

TECHNIQUE

In the past, various techniques for cholangiography have been suggested by Macdonald,[5] Gius and associates,[3] Mixter and co-workers[6] and others. For this series of cholangiograms the following technique was used.

1. The junction of the cystic duct and hepatic duct was cleared of surrounding tissues. The distal cystic duct was tied with No. 20 cotton suture.

2. A small polyethylene catheter was inserted through a small opening in the cystic duct into the common duct, or a cephalic needle (No. 26) on a 10 inch length of polyethylene tubing was inserted through the wall of the common duct with the tip pointing toward the ampulla.

3. All packs, retractors, instruments, and so forth were removed from the operative field and a sterile towel was placed over the wound.

4. A portable x-ray machine was moved into position as directed by the surgeon.

5. The surgeon then injected 10 to 15 c.c. of 35 per cent Diodrast solution through the polyethylene tubing.

6. The surgeon stepped away from the field, the patient's respiration was suspended by the anesthetist and an x-ray was taken with the 80 kilovolt 30 milliampere portable machine, using a stationary grid cassette and cone.

7. The x-ray machine was removed from the field and the cassette removed from under the patient.

8. After the film was developed it was returned while wet and read by the surgeon.

A number of difficulties arose in using this procedure. (1) One or more scout films were taken prior to anesthetizing the patient which often delayed surgery. (2) After a good scout film had been taken and the patient anesthetized, the patient occasionally required some further adjustment of position which made the scout film of no value. (3) Insertion of the needle into the common duct was difficult in some cases. (4) Maintenance of the position of the needle or catheter in the common duct occasionally was difficult. (5) Leakage of the catheters, needles, and puncture sites often was encountered. (6) Sticking of syringes with the Diodrast occasionally occurred even when the Diodrast was warmed. (7) Occasionally time was spent waiting for the x-ray technician to arrive. This delay was caused by his not being in the operating suite or by his taking x-rays in another operating room at the time he was needed for cholangiography. (8) Occasionally the x-ray machine would not operate properly due to mechanical failure or low voltage supplied the machine from the operating room outlets. (9) After the x-ray was taken one of the operating personnel had to raise the sterile drapes on one side of the field and remove the x-ray cassette. When a very obese patient was on the wooden cassette holder it would bend in slightly and great difficulty in removing the cassette was encountered; often 2 or 3 people were required. Occasionally redraping of the patient with sterile drapes had to be done after this procedure. (10) The surgeon would wait sometimes up to 20 minutes for a return of the wet film due to the use of old and slow developer, another technician using the operating room developing tank at the same time, or inexperience on the part of the technician. (11) After the film was ready the surgeon was often unable to get close enough to the view-box to examine the film properly. The view-box was situated at the head of the operating table just over the head of the anesthetist who usually was surrounded by an anesthesia machine, suction apparatus, and equipment cart. Attempts were made to alleviate some of these difficulties but in a teaching institution such as this it was found almost impossible to maintain the changes.

RESULTS

1. A study of the surgeon's operative reports showed that he found 134 of the cholangiograms satisfactory, found 20 unsatisfactory, and made no comment on the rest. Of the 134 satisfactory cholangiograms, the surgeon stated that 24 (18 per cent) were suspicious. Of the 24 suspicious he elected to explore only 18. Of the 110 the surgeon considered negative, 20 were explored for other reasons.

2. All of the cholangiograms were recently re-examined and the following criteria for a diagnostic cholangiogram were established:

a. The x-ray technique must be good.
b. All ducts must be filled and visualized in their entirety.
c. No obscuring opacities must lie over the duct system.
d. The concentration of the dye must be correct.
e. The quantity of the dye must be correct.
f. Dye should be seen entering the duodenum.

Fig. 1.

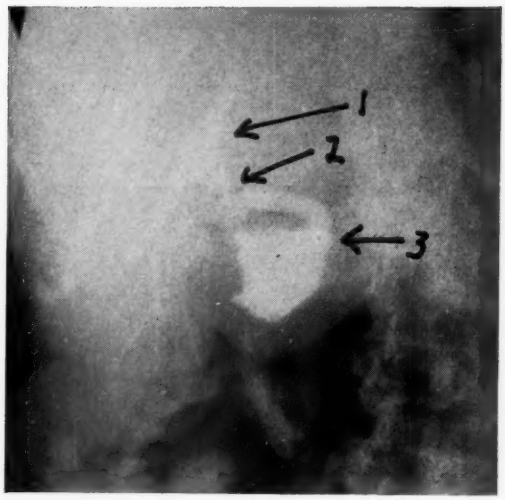

Fig. 2.

Fig. 1.—A satisfactory operative cholangiogram.

Fig. 2.—An operative cholangiogram showing (1) poor visualization of the hepatic ducts, (2) poor filling of the common hepatic duct, and (3) dye in the duodenum obscuring the lower common duct.

Fig. 3.

Fig. 4.

Fig. 3.—Operative cholangiogram which is unsatisfactory because the dye in the dilated ducts is too concentrated. In this case 35 per cent Diodrast was used.

Fig. 4.—Operative cholangiogram showing (1) gall bladder filled with dye by mistake, (2) obscuring of the common hepatic duct by the dye in the gall bladder, and (3) obscuring of the lower common duct by superposition on the vertebrae.

g. Pathology palpated or visualized prior to cholangiography related to the duct system must be seen on the cholangiogram.

It should be noted that any opacity, such as a vertebra or dye pooled under the ducts or dye in the duodenum obscuring the common duct or a portion thereof, may easily give a false cholangiographic study. A cholangiogram is not useful as a routine procedure if no dye is seen entering the duodenum.

Using the above criteria, for evaluating the cholangiograms, 80 that the surgeon reported as being satisfactory were unsatisfactory to totally worthless. Therefore, after re-examination of all of the cholangiograms, 102 were found to be diagnostically unsatisfactory, leaving a total of 66 useful cholangiograms.

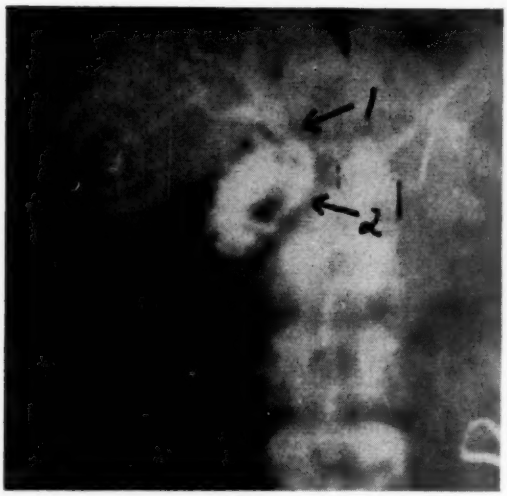

Fig. 5.

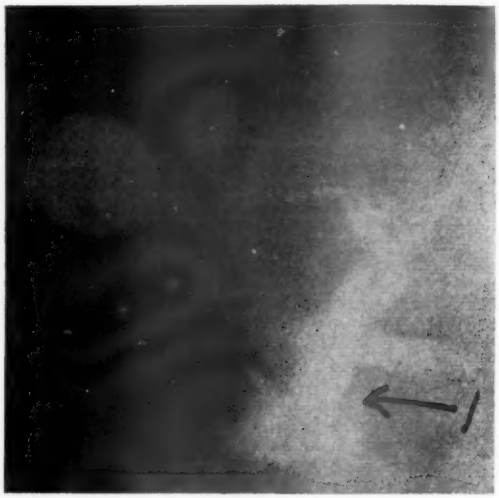

Fig. 6.

Fig. 5.—Cholangiogram showing (1) poor filling of the hepatic (common) duct and (2) obscuring of the lower common duct by dye in the duodenum.

Fig. 6.—Operative cholangiogram showing (1) pooling of dye outside the biliary duct system which obscures the common bile duct.

COMPARISON OF CHOLANGIOGRAPHY WITH COMMON DUCT EXPLORATION

A routine operative cholangiogram was done in 45 cases which also had a common duct exploration. I found 11 of these to be diagnostically unsatisfactory, leaving a total of 32 which were evaluated for accuracy. Table VI shows a comparison of the results of cholangiography and common duct exploration.

TABLE VI. COMPARISON OF THE RESULTS OF CHOLANGIOGRAPHY AND COMMON DUCT EXPLORATION

SHOWED SUSPICION OF STONE ON X-RAY	STONE FOUND ON COMMON DUCT EXPLORATION	NUMBER OF CASES
Yes	Yes	7
Yes	No	8
No	Yes	8
No	No	5
Unable to classify in above groups		4

Table VI shows that 12 (43 per cent) cholangiograms were correct and 16 (57 per cent) were incorrect on common duct exploration.

In the total series of 168 cases which had operative cholangiography, the cholangiogram alone found only 2 unsuspected common duct stones and one intrahepatic gall bladder.

DISCUSSION

There is little doubt that a perfect operative cholangiogram is of tremendous value to the surgeon operating in the area of the biliary system. However, several facts have been brought to light in this review.

1. A great deal of effort and expense were required to set up and perform these 168 cholangiograms. It has been estimated that the average cost per case was around 25 to 30 dollars for the cholangiography, exclusive of any consulting or surgeon's fee.

2. The diagnostic reliability of the satisfactory cholangiogram proved to be very low. This was probably due to one or more of several reasons.

a. Too much dye or too concentrated dye was inserted into the common duct. Diodrast (35 per cent) was used in most of the cases in the series; however, as great a concentration as 70 per cent was used in some. It has been shown by Ashmore and associates[2] that in dogs under ideal conditions using 35 per cent Diodrast, a high percentage of calculi under 5 mm. in diameter are not visualized. From his data, either 17.5 per cent Diodrast or 12.5 per cent Neo-Iopax are the most reliable concentrations of dye to use in dilated or large ducts. We have recently used concentrations of Diodrast as low as 9 per cent with very good results. Of course, this concentration of dye cannot be used in every case.

b. Occasionally the surgeon made some error in the interpretation of the cholangiogram which could easily be accounted for by the fact that most of the surgeons doing the cholangiograms had no particular interest and had no formal instruction in the procedure. In some cases, unavoidable errors in interpretation were made.

c. Occasionally a stone was so small that it could not be resolved on the roentgenogram. This is a defect that cannot be overcome with present x-ray techniques.

d. Several stones were found which were of the same density as the radiopaque media used. This is an important fact which has not been stated before. Actually the surgeon was in error when he did not thoroughly examine the scout film prior to surgery to determine the radiopacity of the stones.

3. The over-all average operating time was prolonged by 41 minutes by the performance of the operative cholangiogram. This time of prolongation certainly did not hold true for each individual case because many of the cases had total operating times of less than one hour. This time did exceed that stated in the literature of from 5 to 25 minutes.[3, 4] An analysis of the time required to do the various steps is as follows:

a. (Surgeon) The cystic and common ducts were cleared for inspection.

b. (Nurse) All of the air was removed from the syringe, tubing, and needle, and the syringe was checked to see that it did not stick. -------- 1 min.

c. (Surgeon) The needle was bent to the desired angle and inserted into the cystic or common duct. ---------- 1 min.
d. (Surgeon) Bile was aspirated and examined. ---------- ½ min.
e. (Surgeon and assistant) All instruments, packs, and other objects were removed from the operative field. ---------- 1 min.
f. (Surgeon and x-ray technician) A sterile towel was placed over the wound and the x-ray machine was moved into position. ---------- 3 min.
g. (Surgeon, anesthetist, and x-ray technician) The dye was inserted, the patient's respiration was suspended and the x-ray was taken. -- 2 min.
h. (X-ray technician) The x-ray machine was removed from the area and the cassette was removed from under the patient. ---------- 2 min.
i. (X-ray technician) The x-ray was taken to the darkroom and developed. ---------- 7 min.
j. (Surgeon) The developed x-ray was examined and interpreted. -- 2-3 min.

This gives a rough estimate of about 20 minutes for the time required to perform the entire cholangiography. Certainly, a surgeon who has had training and experience in this procedure can shorten the time for each step providing his team is working in harmony, whereas the disinterested or untrained surgeon may easily double or triple the time for each step. In any event, difficulty in any step will quickly prolong the procedure.

4. The postoperative morbidity was apparently increased with the performance of an operative cholangiogram, due, probably to one or more of the following reasons.

a. *Prolongation of the Operative Procedure.*—It was found in this series that a prolongation of the operative time by one hour was accompanied by a 3 to 4 per cent increase in the postoperative morbidity.

b. *Increased Number of Nonsterile Personnel in the Operating Room.*—Usually when an operative cholangiogram was performed the only additional person in the operating room was the x-ray technician; however, on occasion there were as many as 8 extra persons in the operating room. This included the x-ray technician, a helper or student with the x-ray technician, visiting surgeons, consulting surgeons, and others. These extra persons in the operating room increased the chances of contamination of the operating personnel as well as the operative field.

c. *Increased Motion in the Operating Room.*—The extra personnel entering and leaving the operating room increased the total motion by a considerable amount. The x-ray technician entered and left the room as many as 8 to 10 times during any one cholangiogram. The operating team usually moved away from the operating table and some of the team even moved to an adjoining room while the x-rays were being taken to avoid exposure to the x-radiation. After the exposure was made the x-ray technician and a helper or nurse crawled under the sterile drapes to retrieve the exposed x-ray film and cassette. This increased motion of the operating team and personnel certainly increased the chances of contamination of the personnel and operative field.

d. *The Introduction of a Dusty Portable X-ray Machine Into the Operating Room.*—Since the operating rooms were not equipped with their own x-ray machines, it was necessary to bring the hospital portable x-ray machines into

the operating room. These machines were in general use over the whole hospital and no attempt was made to clean them before they were brought to the operating rooms. These machines were placed directly over the operative wound to take the cholangiograms (a sterile towel was placed over the wound before the machine was positioned) and at times considerable adjustment was required to attain the correct position.

e. *Spillage of Bile Into the Peritoneal Cavity and Wound.*—Many of the cholangiograms were performed by insertion of a needle through the wall of the common duct and it was observed that as many as 10 or 15 punctures of the wall were made in some cases. (These holes usually were not subsequently closed with suture.) In each case the area was packed to prevent spillage of bile but it was noted that bile leaked into the peritoneal cavity as the drains were placed and the wound closed. It was also noted that during the postoperative period bile drainage was usually greater in those who had had cholangiography than in those who had not had cholangiography. These puncture holes allowed infected bile to flow into the wound not only during the time of surgery but for several days after the surgery was performed, defeating the principle of good surgical technique which demands that the surgeon not only securely tie the cystic duct but also ligate any accessory bile ducts entering the gall bladder directly from the liver.

f. *Removal of the Appendix as an Incidental Procedure.*—From Table V, it can be seen that in this series 99 cases had no incidental appendectomy with a wound infection rate of 4 per cent whereas 87 cases had an incidental appendectomy performed with a wound infection rate of 12 per cent. This gives a statistically significant difference of 8 per cent. There was a tendency for the surgeon to perform an appendectomy during the time he awaited the return of the cholangiogram from the darkroom. In one case the surgeon had enough time awaiting the x-ray to reflect the cecum and remove a retrocecal appendix. This is an unusual occurrence but it did occur. It is therefore felt that when the surgeon has no extra time on his hands he will not perform incidental appendectomy.

g. *Injection of a Foreign Material Into the Liver and Pancreas.*—We know from past experience that cholangitis, pancreatitis, and hepatitis can occur following postoperative T-tube cholangiography, when the dye is inserted too rapidly or under too great a pressure. Usually in the conscious patient the pain caused by distention of the common duct prevents the dye being inserted under too great a pressure. This does not hold true in the anesthetized patient and though no cases of severe cholangitis, hepatitis, or pancreatitis were reported in this series of cases it may have been that they were either overlooked or misdiagnosed. There were 5 cases which had unexplained postoperative temperature elevations for 6 or 7 days following cholecystectomy with cholangiography which could have easily been due to one of these causes. It is interesting to note that in one case the dye was inserted under such great pressure it flowed retrograde into the liver and entered the blood stream and a right nephrogram was obtained.

From a careful review of these cases and personal experience with most of these cholangiograms, I feel that there are certain disadvantages of operative cholangiography which cannot be entirely eliminated by the most competent and careful surgeon. The operation is necessarily prolonged with the associated increased risk to the patient. The postoperative morbidity is increased by the procedure. The operating team and personnel are exposed to x-radiation. The diagnostic reliability of the procedure is far from being 100 per cent correct. The surgeon is often given a false sense of security and disregards the time tested indications for common duct exploration. The number of negative common duct explorations is increased with accompanying increase in morbidity and mortality. These disadvantages seem to far outweight the advantages when cholangiography is done as a routine procedure. This does not mean that the procedure is worthless; far from it. It should be used as an adjunct to time-tested methods for determining the condition of the common duct.

Operative cholangiography should be reserved for use when: (a) an anomaly of the biliary system is found or suspected at surgery, (b) indications for common duct explorations are present, (c) there is a history of pancreatitis (great care must be used in these cases to prevent reactivation of the pancreatitis), (d) there is an indication of disease of the retroduodenal portion of the common duct, and (e) there is a real doubt in the surgeon's mind about the condition of the biliary duct system. If these indications are kept in mind, fewer unnecessary operative cholangiograms will be performed.

SUGGESTED PROCEDURE

A thorough evaluation of the methods used heretofore indicates that the following procedure, if followed in detail will obtain satisfactory cholangiograms in a large percentage of cases. (This is in addition to the normal procedure for cholecystectomy.)

A. Preoperative Preparation.—The surgeon should thoroughly examine the preoperative oral cholecystogram to determine the radiopacity and position of all visible calculi. If a calculus is of the same radiodensity as the dye used the calculus will not be seen on cholangiography (assuming the presence of the calculus in the common duct).

The large bowel should be thoroughly cleansed of feces and gas the night before surgery.

Adequate premedication should be administered. Demerol should be used in preference to morphine since it is felt that the latter may cause spasm of the sphincter of Oddi in some individuals.

B. At Surgery Prior to Anesthetization of the Patient.—The patient is placed in the supine position on the operating table with a rigid x-ray cassette holder under the patient. The left side of the patient is raised about 2 inches by placing a folded sheet under the left side of the patient. If the patient seems to be tilted too far, the table is tilted slightly in the opposite direction. Care should be taken that the table is leveled when the x-ray is taken.

A 10 by 12 grid cassette with film is placed in the proper position in the cassette holder. A moving bucky cassette holder is preferable to the grid cassette if available. If no further movement of the patient is anticipated by the surgeon or anesthetist the patient stops his respiration and a scout film is taken. It has been found that an 80 kilovolt, 30 milliampere x-ray machine with an adequate cone gives very satisfactory results.

The scout film is examined for (a) position (the lower two ribs, the iliac crest and vertebrae should be seen), (b) technique (some soft tissue detail must be seen), (c) radiopaque material (this includes calculi, barium in the gastrointestinal tract and foreign bodies which might interfere with the interpretation of the cholangiogram), and (d) any other pathology which might have not been noted previously.

A fresh film is placed in the cassette and the cassette is again placed in the cassette holder.

The patient is then anesthetized.

C. At Surgery After the Patient Is Anesthetized.—The operation is performed as usual. The junction of the cystic and common hepatic ducts is cleaned and identified. The cystic duct is carefully cleaned. A free tie is placed around the cystic duct one centimeter from the common duct (if possible). The desired quantity and concentration of dye is warmed (to prevent sticking) and placed in a 20 c.c. syringe. A prepared Murphy-Gardner pediatric scalp vein set is attached to the syringe. All bubbles of air are removed from the syringe, polyethylene tubing, and needle. The needle is bent slightly, as desired, and inserted into the cystic duct just below the tie with the tip extending into the common duct. Occasionally the cystic duct is long and descends for quite a way beside the common hepatic duct. In these cases the needle is inserted into the cystic duct and then through the common wall of the cystic and common hepatic ducts. Bile is aspirated and examined. The bile will usually float to the top of the dye and not mix. The packs and instruments are removed from the field. It is wise to suture the drapes to the skin rather than use towel clips when the patient is first draped. A sterile towel is placed over the wound. The operating table is leveled. An x-ray machine which is for operating room use only and which has been thoroughly cleaned is then centered over the junction of the cystic and common hepatic ducts. This is done by the technician as directed by the surgeon. All personnel, besides the surgeon and anesthetist, move out of range of the x-radiation. The anesthetist is protected with a lead apron and lead shield. An adequate amount of 17.5 per cent Diodrast is injected into the duct system. The amount and concentration of the dye are determined by the surgeon when he first inspects the duct system. In dilated ducts (those above one centimeter in diameter) 10 to 20 c.c. of 11 per cent Diodrast may give the best results; however, in small caliber ducts 17.5 or 35 per cent Diodrast may give the best results. Experience and judgment will guide the surgeon in determining the amount and concentration of dye to use in any given case. The surgeon moves out of the field of x-radiation or is adequately protected. The anesthetist holds the patient in apnea and the x-ray is taken when the anesthetist gives him the signal. The surgeon returns to the field and removes the

syringe from the tubing and allows bile to drain out away from the field. The x-ray technician changes the cassettes and another x-ray is taken in the same manner 3 minutes after the first. All personnel return to the operating table and resume the operation. While awaiting the x-ray, exploration can be made, drain stab wounds can be made, or other procedures can be done as desired. Actually, the gall bladder can be removed at this time. The x-rays are returned and examined. If the x-rays are satisfactory, they are interpreted and the operation is resumed.

Some advocate removal of the gall bladder prior to operative cholangiography. However, this has not been found necessary in most cases. The surgeon can usually determine whether or not the gall bladder will overlie and obscure the duct system when he first examines the area.

CONCLUSIONS

Before a surgeon (or group of surgeons) decides to perform operative cholangiography he must (a) become intensely interested in the procedure and instill this interest in his operative team, (b) become well informed and well read on the subject of operative cholangiography, (c) be willing to devote a great deal of time and effort training his team, (d) be flexible in attitude and quickly recognize errors in technique and correct them, (e) understand that at first many of the cholangiograms will be unsatisfactory and even when the team becomes proficient he will not obtain 100 per cent good results, (f) understand that cholangiography is not entirely satisfactory as a routine procedure, (g) realize that satisfactory operative cholangiograms are far from being 100 per cent correct and time-tested indications for common duct exploration should not be ignored, (h) realize that operative cholangiography prolongs the operative time and increases the postoperative morbidity, (i) must fully cooperate with and demand full cooperation from the members of the operating team, and (j) beware of the hazard of x-radiation.

No surgeon can perform operative cholangiography and obtain satisfactory results without intense interest, training, skill, proper equipment, and cooperation of the members of the operating team.

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THE EFFECT OF ANTIBIOTIC AGENTS ON RESIDUAL BILIARY INFECTION

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THIS presentation is a report of the study of bacteria from common duct bile in patients requiring T-tube drainage after biliary surgery. A great deal of this research was carried out on the Fourth Surgical Service at the Boston City Hospital. Special attention was given to the effect of antibiotics on residual biliary infection. Several publications of research material have been presented leading up to the present work dealing with such factors as: (1) the technique of biliary pressure study,[5, 7] (2) postcholecystectomy syndrome,[6] and (3) the relation of bacteria in the bile to biliary dynamics.[8]

From a study of these observations it was obvious to the authors that infection within the biliary tree plays a predominant role in biliary pain.

Evidence collected in a series of studies of patients undergoing T-tube biliary drainage after removal of the gall bladder revealed sufficient information for the following conclusions: (1) 90 per cent of patients requiring T-tube drainage showed evidence of infection in the biliary tree, as indicated by the presence of pathogenic bacteria in the bile; (2) paralleling the presence of bacteria in bile was a sensitivity of the biliary tree to perfusion saline solution—such perfusion produced pain simulating biliary pain; and (3) biliary pain suffered after removal of the gall bladder is due to residual infection in the small radicles of the biliary tree.

Evidence was collected from a study of T-tube patients to indicate that antibiotic therapy, either injected into the biliary tree through a T tube or administered systemically, would help resolve the biliary infection and thereby permit earlier removal of the T tube from the common bile duct.

Preliminary studies by Sarkisian, McGowan, and Wickham[8] showed beneficial effects of streptomycin injected into the T tube. Earlier reports by Zaslow, Counseller, and Heilman[9, 10] regarding antibiotic concentration in bile further stimulated our interest in this direction. Previous observations[3, 7] had established to our satisfaction that prolonged T-tube drainage alone is sufficient to clear up residual biliary infection. However, any process that could speed up resolution of infection and earlier removal of the T tube should be welcome to all persons concerned.

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The purpose of this study, therefore, was to determine the effects of antibiotics on residual biliary infection following removal of the gall bladder. With this in mind, a study was made of patients with T-tube drainage. A study of the following aspects of biliary physiology was made in an attempt to correlate each: (1) residual biliary infection by a study of bacteria in T-tube bile, (2) sensitivity of the biliary tree to pain, as measured by perfusion pain pressure, (3) evidence of biliary obstruction as indicated by resting intrabiliary pressure (studies 2 and 3 are referred to as biliary dynamics), and (4) effect of antibiotic agents on residual biliary infection.

METHODS OF STUDY

Patients who had cholecystectomy and common duct drainage were studied postoperatively as follows: (1) intrabiliary pressure studies (biliary dynamics), (2) cholangiography studies, (3) bacteriologic studies of the duct bile, and (4) effect of antibiotics on (a) biliary dynamics and (b) bacteria in the bile.

All patients in this series were subjected to biliary pressure studies as previously described by one of us (McGowan).[1, 4-7] The first intrabiliary pressure determination was performed on the twelfth to the fourteenth postoperative day and was repeated weekly thereafter until pressures reached normal levels. After biliary dynamics were normal, conditions were considered favorable for removal of the T tube. Sixty patients were studied. Thirty-six of the 60 were found to be satisfactory for general evaluation of biliary dynamics and bacteriologic study, and of these 36, 12 were suitable for antibiotic study.

Biliary Dynamics.—The resting intrabiliary pressure was measured through a manometer filled with saline solution. Pressure was recorded in millimeters of water above the ensiform process, with the patient recumbent. Zero to 30 mm. H_2O above the ensiform was considered normal. A water manometer was connected to the T tube through connecting rubber tubes. A saline reservoir bottle was connected by a Y tube for filling the system and for perfusion of the bile duct. The resting intrabiliary pressure is an index of the patency of the lower end of the bile duct.

Resting intrabiliary pressure is increased in cases of ampulla edema, spasm of the sphincter of Oddi, missed common duct stone, or pressure from the head of the pancreas. When elevated, resting biliary pressure is due to spasm; it is reduced by inhalation of amyl nitrite. In all cases cholangiograms confirmed the information already obtained by the pressure studies. In cases presenting elevated intrabiliary pressures due primarily to edema, there was also present a significant amount of spasm. This averaged approximately a 15 to 20 mm. fall on the manometer after the use of amyl nitrite. Conversely, mechanically obstructed cases revealed no drop in pressure after amyl nitrite inhalations and the initial resting pressure of these cases was significantly higher than in cases with spasm alone.

The perfusion pain pressure was determined by gradually raising intrabiliary pressure until biliary pain was experienced by the patient. Perfusion of the bile ducts was performed by lowering the reservoir bottle to the level

of the fluid in the manometer. The clamp was removed from the tube on the reservoir bottle and the bottle was raised gradually. In this way, the pressure was raised gradually in the biliary tract as well as in the manometer.

Perfusion pain pressure is an index of the sensitivity of the biliary tree and, hence, the degree of residual biliary infection. When the patient can tolerate perfusion pressures of 550 mm. H_2O or more without pain, the bile ducts may be considered free of residual biliary infection.

It was found that, when the perfusion pain pressure became normal, bacteria disappeared from the bile. On the other hand, when the perfusion pain is below 550 mm. H_2O, residual biliary infection is present and the lower the perfusion pressure, the greater the degree of infection.

Bacteriology Study.—Cultures were taken from the T-tube bile of each patient studied. The first postoperative cultures were taken just prior to the first biliary pressure determination, that is, on the twelfth to fourteenth postoperative day.

Results: In the course of this study, 225 cultures of T-tube bile were obtained. The organisms most commonly encountered in the order of frequency were as follows: *Bacterium pyocyaneus, Enterococci, Aerobacter aerogenes, Bacillus proteus, Escherichia coli, Clostridium welchii,* and *Streptococci alpha.*

Table I reveals the incidence of these organisms found in 36 of the cases studied.

TABLE I. THE BACTERIA FOUND ON CULTURE, IN ORDER OF FREQUENCY, FROM THE T TUBES OF 36 PATIENTS, 14 DAYS POSTOPERATIVELY

BACTERIA	NUMBER OF PATIENTS	PER CENT OF TOTAL
Bacterium pyocyaneous	28	77
Enterococci	25	69
Aerobacter aerogenes	20	55
Escherichia coli	15	42
Bacillus proteus	12	33
Clostridium welchii	8	22
Streptococcus alpha	6	17

Twenty-three (64 per cent) of the 36 cases evaluated revealed positive cultures of *Escherichia coli* at some time during their postoperative course, although only 15 of these had positive cultures of *Escherichia coli* on the fourteenth postoperative day.

Twelve of the 36 (33 per cent) presented positive cultures of *Clostridium welchii* at some time during the study, although only 8 of these were initial cultures taken on the fourteenth postoperative day. Nine of the 36 (25 per cent) revealed both *Escherichia coli* and *Clostridium welchii.*

All patients presenting cultures of *Escherichia coli* and *Clostridium welchii* in the bile, together or separately, were found to have abnormal biliary dynamics, indicative of residual biliary infection. Either the resting pressure levels or the pain perfusion levels were found to be abnormal, and in approximately one-half of the cases observed presenting *Escherichia coli* and/or *Clostridium welchii* in the bile, both the pain perfusion and the resting pressure levels were abnormal.

The highest resting pressure recorded was 160 mm. H_2O above the ensiform (normal 0 to 30 mm. H_2O). This high resting pressure occurred in 2 cases. *Escherichia coli* was found as the sole bacteria in both cases. When the biliary dynamics returned to normal, the cultures were found negative for *Escherichia coli.* Apart from the cases with either *Escherichia coli* or *Clostridium welchii,* there were no other instances of such markedly disturbed biliary dynamics except in 3 patients who subsequently proved to have retained calculi in their common duct.

The average resting intrabiliary pressure on the fourteenth postoperative day was found to be 93 mm. H_2O (normal 0 to 30 mm. or less) in these cases in which *Escherichia coli* or *Clostridium welchii* were cultured. In the cases with either or both bacteria, the average pain perfusion level was 348 mm. H_2O (normal above 550 mm. H_2O) indicating residual biliary infection. The findings in 3 patients in particular are worthy of special attention. In these 3 cases, bacteria persisted in the bile after the biliary dynamics had returned to normal levels. One of these cases showed *Escherichia coli* and *Clostridium welchii* and the remaining 2 showed *Escherichia coli* alone. None of these had antibiotics, and all required prolonged drainage before bacteria finally disappeared.

Patients who tolerated perfusion pressures up to 550 mm. H_2O were considered free from infection. The lower the perfusion pain pressure, the greater the infection. Therefore, 160 mm. perfusion pain pressure is indicative of severe residual biliary infection. The presence of 2 organisms, *Clostridium welchii* and *Escherichia coli* together in duct bile and associated biliary dynamics can be considered as pathogenic and indication for prolonged T-tube drainage.

No appreciable change in biliary dynamics was apparent in regard to *Bacterium pyocyaneus, Aerobacter aerogenes, Bacillus proteus,* and *Enterococci,* either with or without antibiotic therapy. These bacteria disappeared and recurred with irregular frequency, and their presence did not appear to hinder convalescence or be a factor in abnormal findings such as disturbed biliary dynamics. Although *Aerobacter aerogenes* did not appear pathogenic in the cases in general, Case 2 (below) seems an exception. Here, the appearance of *Aerobacter aerogenes* is associated with disturbed biliary dynamics.

Antibiotic Therapy.—Six patients receiving Terramycin therapy and 6 receiving streptomycin therapy were adequately followed. Streptomycin was administered only to hospital patients and Terramycin to outpatients.

Technique of administration of streptomycin is as follows. One gram of streptomycin powder was thoroughly mixed with 20 c.c. of sterile saline solution. Twice daily 10 c.c. of this solution was injected into the T tube, and the tube was clamped off for a 4-hour period. The injection of streptomycin was carried out daily for 5 days. The average effect on biliary pressure studies on 6 cases receiving streptomycin into the common duct was significant, as may be observed in Fig. 1.

In the 6 patients receiving streptomycin, there was a more rapid return to normal of the perfusion pain pressure than in a control group. The bile

duct could be perfused with higher pressures earlier without pain in the streptomycin-treated cases.

Resting intrabiliary pressure: The group receiving streptomycin into the T tube showed a more rapid return of the resting intrabiliary pressure to normal than did the group not receiving streptomycin.

The conclusion of this phase of study is that residual biliary infection, as measured by perfusion pain pressure, is accompanied by obstruction to the flow of bile by duodenal spasm or ampulla edema. As residual biliary infection undergoes gradual resolution with T-tube drainage, the biliary dynamics return to normal and bacteria disappear from the bile. Resolution of residual biliary infection is speeded up by injection of streptomycin into the biliary tree through an indwelling T tube.

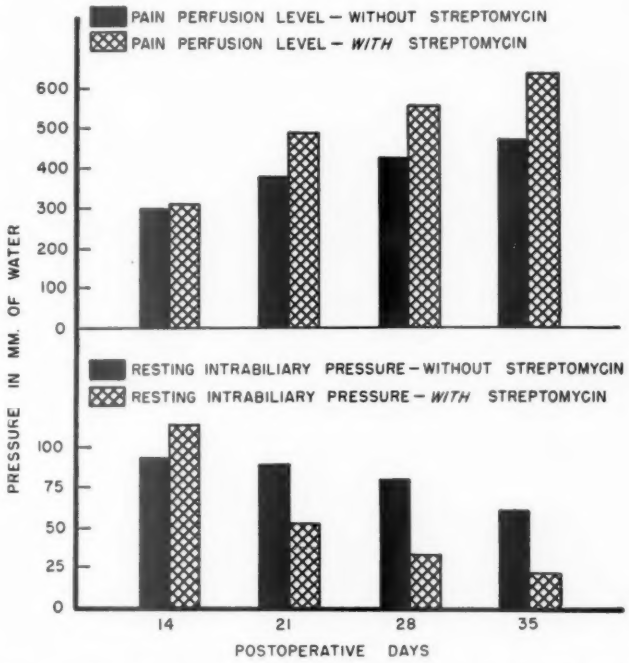

Fig. 1.—This represents the correlation between the pain perfusion levels and the resting intrabiliary pressure of a series of 6 patients with streptomycin injected into the bile ducts through a T tube and 6 patients on T-tube drainage without streptomycin. The intrabiliary pressures were averaged on the fourteenth, twenty-first, twenty-eighth, and thirty-fifth postoperative days. The upper part shows that the tolerance to pain on perfusion increased with the streptomycin group (normal 550 mm. H_2O or more). Note in the lower part of the graph that the resting intrabiliary pressure (normal 0 to 30 mm. H_2O), while higher in the streptomycin-treated group on the fourteenth day (before treatment), improved more rapidly than the controls. The treated cases, on an average, had pressure levels on the twenty-first day equal to the untreated cases on the thirty-fifth day.

Terramycin* (oxytetracycline) was administered by the oral route. Therapy was usually begun 14 days postoperatively. The dosage consisted of 500 mg. every 6 hours for 5 days. The total amount of Terramycin per patient amounted to 10 grams. The resulting biliary pressure dynamic changes are illustrated in Fig. 2. The results from the use of oral Terramycin on 6 patients were almost exactly similar to the comparative studies of the cases receiving

*Terramycin in this study was supplied by Charles Pfizer & Co., Inc., 630 Flushing Avenue, Brooklyn 6, N. Y.

streptomycin and the controls. Oral Terramycin speeded up resolution of the residual biliary infection as manifested by improvement in tolerance to perfusion pain pressure in the common bile duct. As residual biliary infection subsided, the resting intrabiliary pressure also returned to normal.

Clinical evaluation: It is of interest to note that, of the 36 patients evaluated, 34 presented pathologic reports of cholecystitis, 32 cholelithiasis, and 16 choledocholithiasis. Jaundice was present in 24 cases, and pancreatitis was noted at operation in 6 cases.

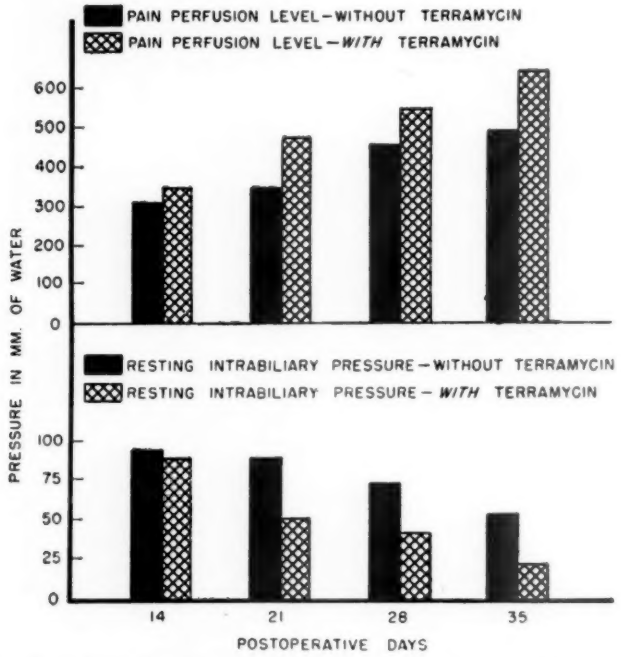

Fig. 2.—This represents the comparison between pain perfusion levels and resting intrabiliary pressure of a series of 6 patients treated with oral Terramycin and 6 untreated patients. The average pressures were tabulated on the fourteenth, twenty-first, twenty-eighth, and thirty-fifth postoperative days. The Terramycin-treated cases showed pressure levels as good on the twenty-first day as the cases on T-tube drainage alone showed on the thirty-fifth day, indicating earlier resolution of infection in the cases given Terramycin.

CASE REPORTS

CASE 1.—Mrs. L. O., a 68-year-old woman, was admitted to the Fourth Surgical Service of the Boston City Hospital. On admission she complained chiefly of severe "knifelike" pain in the upper right quadrant of the abdomen with radiation into the mid-dorsal and right scapular region. She presented a past history of similar, but milder, attacks during the past 6 years, which occurred approximately once every 2 to 3 months and which were usually relieved within 2 hours by the application of a hot water bottle to the abdomen. There was no nausea or vomiting during the previous attacks or during her admission attack. She had never noticed jaundice, chills, fever, or distention; however, fatty, fried foods caused epigastric distress.

Physical examination revealed tenderness and spasm of the right upper quadrant of the abdomen. Laboratory studies revealed the urine to contain albumin, grade 3, 4-6 R.B.C., 5-8 W.B.C. Blood studies revealed: W.B.C.—10,000, hemoglobin—12.5 Gm., urinary diastase—negative.

The acute attack subsided under therapy and a cholecystogram revealed a nonfilling gall bladder. Operation was performed on Sept. 12, 1950. The gall bladder was removed

and was found to contain one calculus measuring 0.5 cm. in diameter impacted in the cystic duct. The common bile duct was large and distended and needle aspiration revealed cloudy bile. Exploration of the common bile duct revealed no calculi and a McGowan-Keeley T tube was inserted into the common bile duct for prolonged biliary drainage.

Thirteen days postoperative, Sept. 12, 1950:

Bile culture: *Clostridium welchii, Bacterium pyocyaneus, Bacillus proteus,* and *Aerobacter aerogenes.*
Biliary pressure studies: resting intrabiliary pressure = 110 mm. H_2O (normal 30 mm. or less).
Interpretation: moderate degree of biliary obstruction.
Perfusion pain level: 400 mm. H_2O (normal 550 mm. or more).
Interpretation: slight residual biliary infection.
Streptomycin One Gram intraductally for 5 days (total of 5 grams)

Oct. 3, 1950:

Bile culture: *Bacterium fecalis alcaligenes, Clostridium welchii.*
Resting intrabiliary pressure: 80 mm. H_2O (normal below 30).
After amyl nitrite: 55 mm. (normal below 30).
Interpretation: partial drop after amyl nitrite indicates some spasm of the sphincter of Oddi and some edema of the ampulla.
Perfusion pain pressure: 600 (normal + 550 or more, indicating less infection).
Interpretation: no residual biliary infection.

Oct. 15, 1950:

Bile culture: *Bacterium pyocyaneus, Bacillus proteus,* and *Enterococci.*
Biliary resting pressure: 50 mm. (normal 0 to 30).
After amyl nitrite: 50 mm. (normal 0 to 30).
Interpretation: slight biliary obstruction due to ampulla edema.
Perfusion pain pressure: +600 mm. H_2O (normal +550).
Interpretation: no residual biliary infection in the radicles of the biliary tree.

Nov. 2, 1950:

Bile culture: *Bacterium pyocyaneous, Aerobacter aerogenes.*
Biliary resting pressure: 45 mm. (normal 0 to 30).
After amyl nitrite: 30 mm.
Interpretation: slight spasm of the duodenum; no ampulla edema.
Perfusion pain pressure: 575 (normal 550 or over).
Interpretation: no residual infection in the biliary tree.

Nov. 9, 1950:

Bile culture: *Bacterium pyocyaneus.*
Biliary pressure: resting biliary pressure = 30 mm. (normal 0 to 30).
After amyl nitrite: 30 mm. (normal 0 to 30).
Perfusion pain pressure: +600.
Comment: normal biliary dynamics, conditions suitable for removal of T tube, *Bacterium pyocyaneus* nonpathogenic or contaminant.

The patient remained asymptomatic and the T tube had been continuously clamped for one week. The tube was removed.

Comment: It should be noted that both her pain perfusion level and resting intrabiliary pressures rapidly approached normal levels after treatment with streptomycin as contrasted to untreated cases which, on an average, required twice as much time to reach normal pressure levels.

CASE 2.—Mrs. M. C., a 48-year-old housewife, was admitted to the hospital on Aug. 4, 1950. Her chief complaint was constant sharp right upper quadrant pain of 8 hours'

duration. Past history had been negative, except for frequent attacks of nausea and vomiting and intolerance to fatty foods of one month's duration. Nausea was relieved by copious vomiting; attacks were associated with epigastric and right upper quadrant pain, aggravated by narcotics. The day of admission she noticed jaundice, clay stools, and dark brown urine.

Physical examination was negative, except for the skin which showed clinical jaundice. Abdominal examination revealed distention and moderate tenderness to palpation in the epigastrium and right upper quadrant.

Laboratory studies revealed: icteric index 50, hemoglobin 11 Gm., W.B.C. 19,800, blood urea nitrogen 10, carbon dioxide combining power 53 mg., blood chlorides 82 mg. per cent, total serum proteins 6.4 per cent.

Under therapy the attack subsided, as did the jaundice. Cholecystogram revealed a poorly functioning gall bladder with visible calculi. Cholecystectomy and choledochotomy were performed Aug. 24, 1950. Two mulberry calculi, measuring 1 cm. in diameter, were found in the gall bladder. No mechanical obstruction was found in the common bile duct. Evidence of pancreatitis was present.

On Aug. 29, 1950, the patient experienced the sudden onset of severe precordial pain. A diagnosis was made of coronary occlusion by the consulting cardiologist. Biliary pressure studies were delayed for this reason until Sept. 25, 1950, 32 days postoperatively.

Sept. 25, 1950:

Bile culture: *Aerobacter aerogenes* and *Bacterium fecalis alcaligenes.*
Biliary resting pressure studies: 50 mm. H_2O (normal 0 to 30 mm.).
Interpretation: slight biliary obstruction.
Perfusion pain pressure: 540 mm. H_2O (normal 550 mm. or more).
Interpretation: slight residual biliary infection.

Oct. 5, 1950:

Bile culture: *Bacterium pyocyaneus, Bacillus proteus,* and *Aerobacter aerogenes.*
Biliary resting pressure: 80 mm. H_2O (normal 0 to 30 mm.).
Interpretation: moderate biliary obstruction.
Perfusion pain pressure: 350 mm. (normal over 550 mm.).
Interpretation: moderately severe residual biliary infection which has increased considerably since previous test.

Weekly cultures and pressure determinations remained essentially the same, with slight variations until Nov. 1, 1950, when this patient experienced a recurrent mild coronary attack at home.

Dec. 7, 1950:

Bile culture: *Bacterium pyocyaneus, Bacillus proteus,* and *Enterococci.*
Biliary resting pressure: 90 mm. H_2O (normal 0 to 30 mm.).
Interpretation: moderate biliary obstruction.
Perfusion pain pressure: 450 mm. H_2O (normal over 550 mm.).
Comment: slight residual biliary infection.

Dec. 28, 1950:

Bile culture: *Bacterium pyocyaneus, Bacillus proteus, Enterococci,* and *Aerobacter aerogenes.*
Biliary resting pressure: 130 mm. H_2O (normal 0 to 30 mm.).
Interpretation: sharp increase in biliary obstruction.
Perfusion pain pressure: 370 mm. H_2O (normal over 550 mm.).

Comment: With the reappearance of *Aerobacter aerogenes,* dynamics have become much worse. At this point, the patient was administered Terramycin, 2 Gm. daily for 5 days.

Jan. 4, 1951:

Bile culture: *Bacterium pyocyaneus* and *Bacillus proteus.*
Biliary resting pressure: 25 mm. H_2O (normal 0 to 30 mm.).
Perfusion pain pressure: 400 mm. H_2O.

Comment: Return of dynamics toward normal after 6 days of Terramycin appears dramatic. Disappearance of *Aerobactor aerogenes* indicates that it was a pathogen in this case. *Bacillus proteus* and *Bacterium pyocyaneus* were probably nonpathogenic. Biliary dynamics remained normal and the T tube was removed after 3 weeks of continuous clamping of the tube.

DISCUSSION

Table II shows a comparison of the types of bacteria found in 2 successive studies conducted under very similar conditions at the same hospital by Sarkisian and McGowan[8] and one year later by us, the latter of which study is reported in this paper.

TABLE II

SARKISIAN AND MC GOWAN[8]—21 CASES (JULY 1, 1949–JUNE 30, 1950)		CARRIGAN AND MC GOWAN—36 CASES (JULY 1, 1950–JUNE 30, 1951)	
BACTERIA IN ORDER OF FREQUENCY	PER CENT OF TOTAL	BACTERIA IN ORDER OF FREQUENCY	PER CENT OF TOTAL
1. *Escherichia coli*	62	1. *Bacterium pyocyaneus*	77
2. *Bacillus proteus*	38	2. *Enterococci*	69
3. *Aerobacter aerogenes*	28	3. *Aerobacter aerogenes*	55
4. *Bacterium pyocyaneus*	24	4. *Escherichia coli*	41
5. *Clostridium welchii*	14	5. *Bacillus proteus*	33
		6. *Clostridium welchii*	22
		7. *Streptococcus alpha*	10

It will be noted that the relative position of *Escherichia coli, Bacillus proteus,* and *Clostridium welchii* is the same in both series. In the second series, the *Bacterium pyocyaneus* moved from fourth place in the first series to first place in the second. The *Enterococcus* seems to be a newcomer to the second series and has started in second place. There is a possibility that the increase in *Bacterium pyocyaneus* and the appearance of *Enterococcus* is due to the fact that the broad spectrum antibiotics had come into popular use during the time these studies were being conducted. It is quite possible that the change in the intestinal flora, as a result of broad spectrum antibiotics, had brought about this change in the bacteria found in the common duct on T-tube drainage.

Table III indicates the time relation of introduction of broad spectrum antibiotics to this study.

TABLE III. RELATION OF BILE BACTERIA TO ANTIBIOTICS*

Aureomycin released in November, 1948
Study I started July, 1949
Chloromycetin released in October, 1949
Terramycin released in March, 1950
Study I completed June 30, 1950

*This information was provided by the companies detailing the products mentioned.

In the series of Sarkisian and McGowan, the bile became bacteria-free more readily. The bacteria studied in the second series may have become more resistant and therefore more difficult to eliminate, as a result of wide use of broad spectrum antibiotics.

From a review of the literature, the indications are found that bacteria in the common bile duct are more often found in the presence of stones. Stones form when the chemical constituents of bile can no longer be held in solution.

Precipitates occur in bile when the bile acids are split by bacteria and can no longer perform their function of keeping chemicals in solution. This process is reversed by a new synthetic choleretic agent (Zanchol*). In a previous publication by one of us (McGowan),[2] the changes in bile brought about by Zanchol were reported. This choleretic agent brought about marked and apparently beneficial changes in the characteristics of T-tube bile in a matter of 1 to 4 days. The T-tube bile in the average case of residual biliary infection is canary yellow in color and contains a great deal of sediment, consisting of bilirubin crystals, bacteria, and, at times, pus. After 24 hours of Zanchol, administered orally, the bile becomes a brilliant green in color and more transparent. The sediment gradually disappears, so that after 5 days no sediment can be found on microscopic examination of centrifuged specimens of T-tube bile.

This characteristic of Zanchol in putting precipitates in solution should be of value in eliminating bacteria from the bile ducts.

SUMMARY AND CONCLUSIONS

1. The bacteria in the bile were studied in a total of 60 patients who had had cholecystectomy and common duct drainage.

2. The type of organisms cultured from common duct bile collected postoperatively from patients on T-tube drainage are here tabulated in order of frequency. The large majority of bacteria are probably of intestinal origin and, of this group, *Escherichia coli* and *Clostridium welchii* appear to be strongly pathogenic in the biliary tree.

3. Intrabiliary pressure studies were made on all cases studied postoperatively. Disturbed biliary dynamics paralleled the finding of pathogenic bacteria in the bile.

4. As the biliary dynamics returned to normal, the bacteria disappeared from the bile.

5. The signs of residual biliary infection disappeared gradually with prolonged common duct drainage with a McGowan-Keeley T tube.

6. Streptomycin into the T tube speeded up resolution of residual biliary infection. Biliary dynamics returned to normal earlier than in control cases, permitting earlier removal of the McGowan-Keeley T tube.

7. Terramycin, administered orally, proved equally as efficacious as streptomycin in speeding resolution of residual biliary infection.

8. A new choleretic agent, Zanchol, which acts as a bile detergent, brings about changes in the character of bile, which indicates that it should be beneficial in treatment of residual biliary infection.

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STUDIES IN AMMONIA METABOLISM

III. The Experimental Production of Coma by Carotid Arterial Infusion of Ammonium Salts

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THERE is as yet no agreement as to the exact relationship between elevated blood ammonia concentrations and the coma that commonly occurs during hepatic failure. Although ammonia accumulates in the blood during hepatic failure and ammonia (or meat) intoxication can be produced under various conditions, the evidence is not conclusive that ammonia per se is the toxic substance in liver coma.[5]

The purpose of this study is to determine whether or not the experimental production of an elevated cerebral blood ammonia level will produce coma and to determine the factors which influence the onset of such coma. The following paper[2] concerns an investigation of the cerebral biochemical lesions that occur during such ammonia intoxication.

MATERIALS AND METHODS

A total of 103 adult mongrel dogs were used in this study. The experimental infusions varied as shown in Table I. In 35 experiments equal volumes of 5 per cent glucose in water were infused into the carotid artery of the animal which served as a control.

Table I. Summary of Experiments

6 animals—Ammonium chloride 1 to 5 per cent
8 animals—Ammonium citrate 1 to 8 per cent
38 animals—5 per cent glucose in water—controls
51 animals—Ammonium hydroxide 1 per cent plus hydrochloric acid to pH 8.0 to 8.7 in Ringer's lactate solution
4 animals—Infusion stopped to determine reversibility of coma
9 animals—Blood pH altered by separate simultaneous sodium bicarbonate infusion
6 animals—Bicarbonate infusion throughout experiment
3 animals—Bicarbonate infusion after onset of coma
30 animals—Ammonium salt infusion alone
8 animals—Experiment—altered variously by pretreatment with thyroxine; 100 per cent O_2 inhalation during coma
Total—103

Twenty-four hours prior to the infusion of the ammonium solutions the animal was lightly anesthetized with intravenous sodium pentobarbital and a

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unilateral cranial flap was reflected from the zygomatic arch to the sagittal suture. The dura was left intact, the bone flap replaced, and the scalp loosely approximated over the defect with a few skin sutures.

Through a small lateral cervical skin incision a polyethylene catheter was threaded cranially into the common carotid artery and kept in place by a 5-0 silk suture in the arterial wall and anchored to the skin with another suture. A 1.5 cm. long siliconized cast polyester resin T tube was then inserted into a slit in the accompanying external jugular vein and was similarly anchored to the vessel. A polythene plastic tube, 20 cm. in length, was attached to the free arm of the T tube, was brought out the wound, and anchored to the skin with a suture. Both tubes were filled with a saline-heparin solution and the free ends suitably sealed with rubber bands. An encircling plaster of Paris collar was then applied to enclose the 2 tubes and to avoid their dislodgement. One gram of dihydrostreptomycin and 250,000 units of penicillin were administered immediately following operation. The animal was allowed a standard kennel ration and fluids thereafter.

Twenty-four hours after the animal had recovered from these procedures, the encircling cervical plaster was removed and an infusion was begun into the carotid cannula of the unanesthetized animal. The pressure necessary for such an arterial infusion was attained by the use of a sphygmomanometer rubber bulb attached to the air inlet of an ordinary infusion bottle.[6]

The jugular vein cannula was utilized to obtain samples of venous blood which had circulated through the brain, the cannula being kept patent by a very slow (3 to 4 Gtt. per minute) infusion of 5 per cent glucose in water.

Peripheral blood samples were obtained from an indwelling cannula inserted into a femoral vein and fitted with a stylet.

At 30-minute intervals blood samples from both the femoral and jugular veins were drawn into heparinized syringes and immediately tested for ammonia content and pH. A modification of the Conway microdiffusion technique[4] was used for ammonia concentration and a Beckman photometric unit No. 290-31 was used for direct blood pH measurements.

During the experiment a record was made of the respiratory rate, the level of consciousness, evidence of muscle hypertonicity, hyperreflexia, convulsions, and, finally, the time of coma.

Five to 7 minutes after the onset of frank coma in the ammonia infused animals and after a similar time period in the controls, the scalp sutures were quickly removed from the preparatory craniotomy and the dura exposed. A long cruciate incision was then made in the dura, and a 5 to 10 Gm. sample of underlying brain tissue was scooped out with a brain spoon and immediately immersed in liquid nitrogen for subsequent biochemical analysis.

The infusion solutions employed as shown in Fig. 1 were designed to produce both a varying pH and an alteration in the anion employed with the ammonium salt. Isotonic glucose was infused at the same rate as the ammonium salt solutions to rule out water intoxication as the cause of the neurologic abnormalities.

In 7 animals rendered comatose by ammonium salt infusion, the brain was examined microscopically for changes in the astrocytes which are said to be characteristic of hepatic coma.[1]

In 9 experiments the pH of the blood was altered by the infusion of 5 per cent sodium bicarbonate solution in addition to the ammonium salt infusion. In 6 experiments the bicarbonate infusion was continued throughout the experiment, thereby keeping the blood pH essentially within normal limits. In 3 other experiments the bicarbonate infusion was begun only after the animal was in coma. In order to determine whether reversal of the accompanying acidosis would also reverse the coma, peripheral venous blood pH was monitored at 5 to 10 minute intervals in the last series of experiments.

RESULTS

Infusion of 5 per cent ammonium chloride resulted in coma within 2 to 4 hours, with the jugular blood pH falling to less than 6.5 in some cases. A typical experiment employing ammonium chloride is illustrated in Fig. 1.

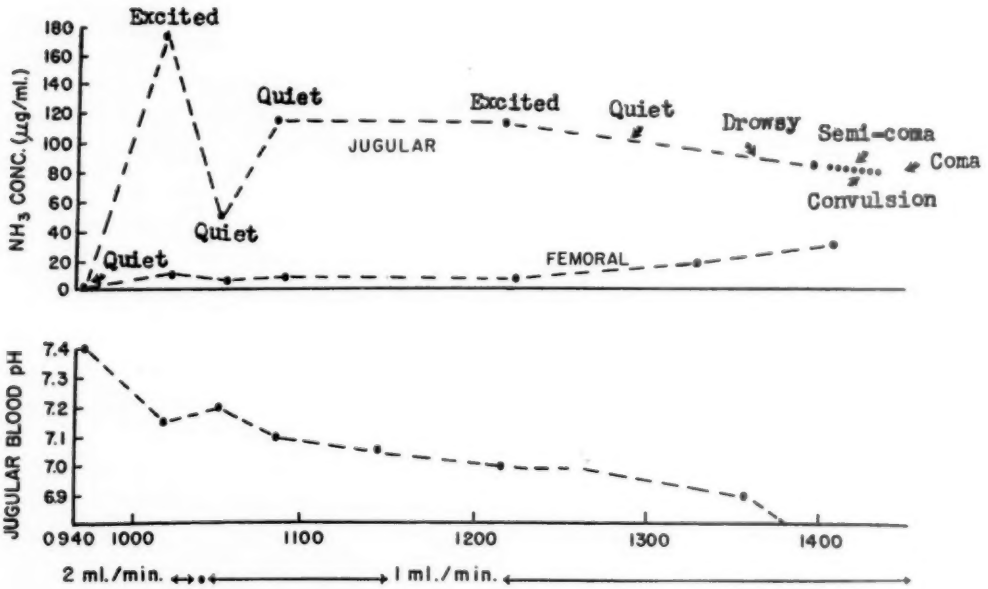


Fig. 1.—Coma produced by carotid infusion of 5 per cent ammonium chloride. Note marked acidosis and precoma rise in femoral venous blood ammonia concentration.

In order to exclude acidosis as the prime cause of coma, other ammonium salts were employed. Ammonium citrate 4 per cent (Fig. 2) was used in 5 experiments, but it produced both acidosis and behavioral changes that suggested a direct irritative effect on the tissues and was therefore not further investigated. Ultimately a standard infusion mixture of 4 per cent ammonium hydroxide in Ringer's solution (neutralized to pH 8.2 to 8.4 with HCl) was used as a routine alkaline ammonium infusate. A typical experiment employing such an infusion is illustrated in Fig. 3.

The results of 26 such infusions of alkaline ammonium solutions in Ringer's lactate solution are shown in Table II and indicate the following.

1. Coma is not dependent solely upon a given critical carotid blood ammonia concentration. Although the experiments were designed to elevate the

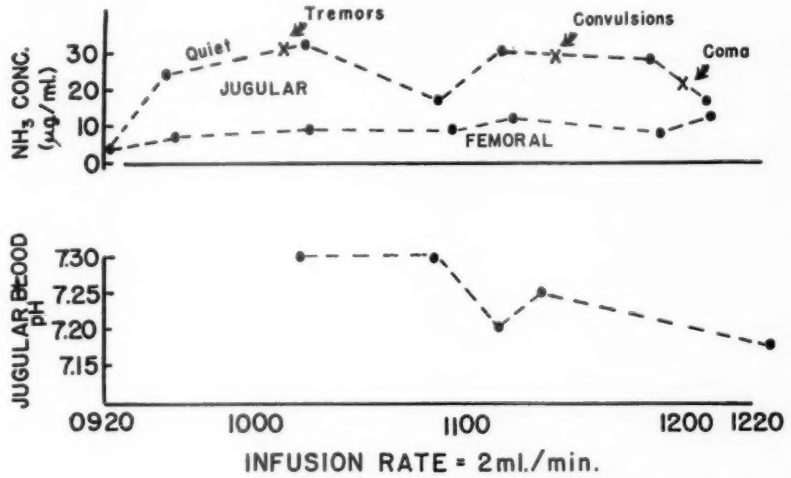


Fig. 2.—Coma produced by carotid infusion of 4 per cent ammonium citrate.

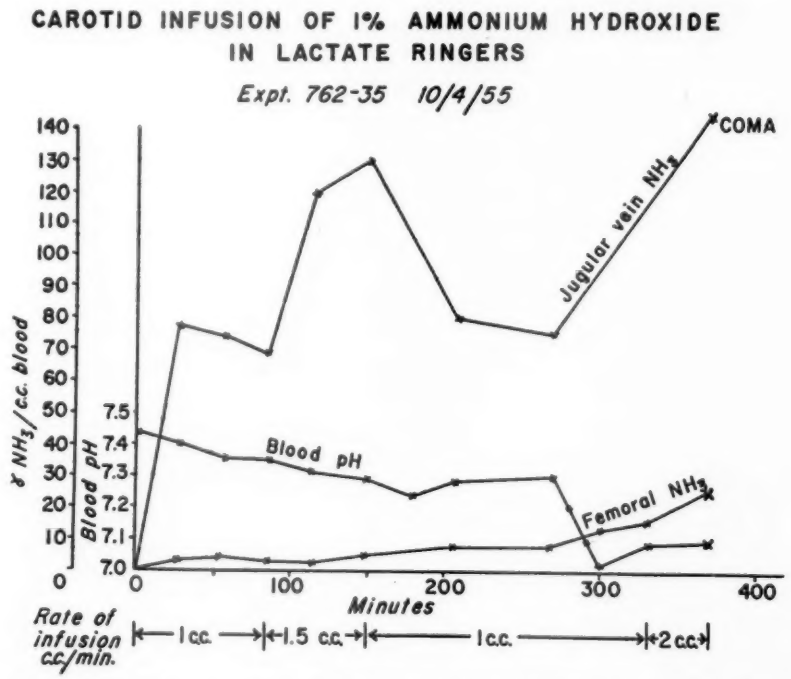


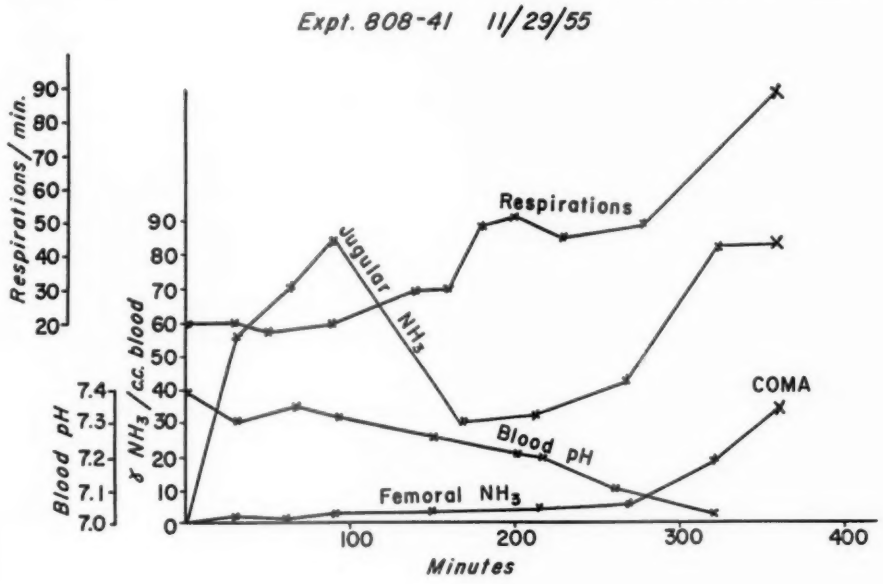
Fig. 3.—Coma produced by typical alkaline (pH 8.55) carotid ammonium salt infusate. Note acidosis and precoma rise in femoral blood ammonium concentration.

carotid ammonia levels far beyond the physiologic range in order to precipitate early coma, dogs tolerated such unilateral carotid ammonia perfusion of blood containing 5 to 75 times the normal ammonia concentrations without undue neurologic change.

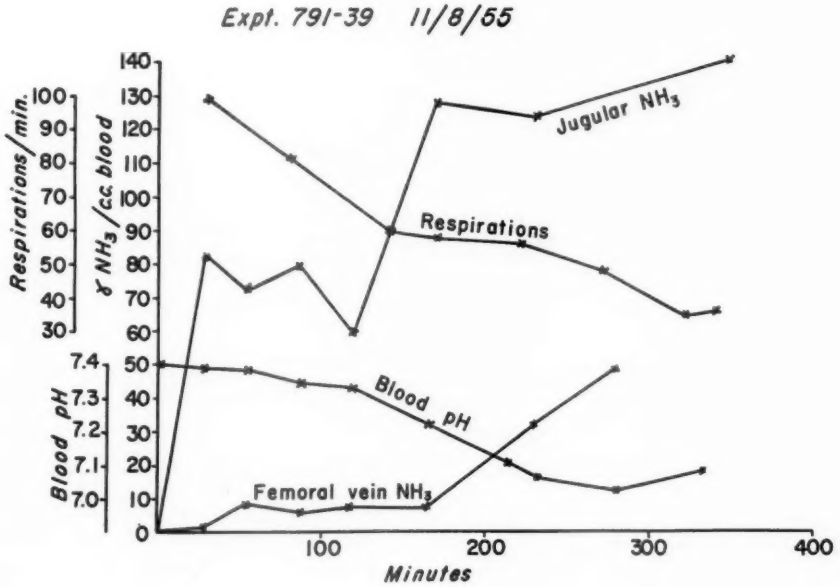
TABLE II. CAROTID INFUSION 1 PER CENT AMMONIUM-HYDROXIDE IN RINGER'S LACTATE

CASE NO.	DOG NO.	DATE	pH INFUSION MIXTURE	pH PERIPHERAL BLOOD			μg NH_3/C.C. JUGULAR BLOOD			BLOOD			TIME pH FALL TO COMA (MIN.)	TIME FEMORAL VEIN NH_3 RISE TO COMA (MIN.)
				100 MIN.	200 MIN.	300 MIN.	100 MIN.	200 MIN.	300 MIN.	TIME TO COMA (MIN.)	pH AT COMA	LEG VEIN NH_3 AT COMA		
1	774-37	10/18/55	8.70	7.40	7.25	7.08	68	108	118	390				
2	768-36	10/11/55	8.55	7.28	7.24	7.20	36	64	95	420				
3	808-41	11/29/55	8.45	7.42	7.29	7.12	84	32	82	360	7.12	18	76	18
4	791-39	11/8/55	8.28	7.34	7.12	7.02	81	124	>175	360	7.08	48	120	20
5	784-38	10/25/55	8.35	7.30	7.28	7.18	19	15.8	32	240	7.18	10	40	10.3
6	829	12/13/55	8.00	7.31	7.19	6.94				235	6.94	9.82	120	10
7	807-40	11/23/55	8.00	7.31	7.02		33	46		210	7.02	14.00	60	60
8	819-42	12/6/55	8.11	7.14	6.68		18	131		240	6.68	21.6	180	80
9	936	3/14/56	8.49	7.38	7.40	7.21				340	7.21			
10	951	4/10/56	7.83	7.30	7.24	7.00				300	6.84		150	
11	652	5/24/55	8.68	7.48	7.39	7.2	23	109	85	420	7.28	24.0	40	30
12	762-35	10/4/55	8.55	7.34	7.23	7.31	69	130	155	330	7.28	15	0	40
13	1-78	8/13/56	8.22	7.30						90	7.30	14	0	10
14	944	4/24/56	8.04	7.40	7.38	7.27	48			360	7.27		0	
15	610	4/14/55	7.75	7.38	7.35	7.25	19	6.8	76	380	6.95		10	
16	611	4/19/55	8.60	7.50	7.40	7.32	34	49	>160	420	7.50	16	0	0
17	618	4/21/55	8.7	7.67	7.47	7.40	98	145	61	500	7.33	7.1		
18	632	5/3/55	8.5	7.42	7.19	7.12	80	82	57	420	6.90	64	246	10
19	908	2/15/56	8.2	7.40	7.24	7.14	7.8	87		340	7.14		120	
20	864	2/8/56	8.22	7.25	7.03	6.94	13.8	8.0	14.7	300	6.94		240	
21	655	6/1/55	8.20	7.40	7.22	7.16	21	33	62	480	7.02	37	180	23
22	587	6/7/55	8.26	7.51	7.38	7.19	23	82	176	600	7.07	>9.2	240	
23	656	6/7/55	8.38	7.46	7.31	7.19	56	53	>190	380	7.19	12.0	60	40
24	1-50	7/25/56	8.30	7.49	7.41	7.05	53	52	47	360	7.05	14.3	90	30
25	980	5/8/56	8.16	7.43	7.30					280	7.30		0	
26	603	4/12/55	8.45	7.52	7.51	7.52	16	48	47	420		11.0		

2. Coma was invariably preceded by an elevation in the peripheral venous ammonia concentration, which characteristically occurred 2 to 4 hours after the start of the infusion and preceded coma by less than 60 minutes. Coma



A.



B.

Fig. 4.—Coma produced by carotid alkaline ammonium infusions (*A*) with subsequent increased respiratory rate (pH 8.45) and (*B*) with subsequent decreased respiratory rate (pH 8.28).

apparently is produced only when the blood ammonia concentration in both carotid arteries is elevated. Under the conditions of this experiment, such did not occur until the ammonia load exceeded the hepatic reserve for conversion of ammonia to urea.

3. The production of coma was independent of peripheral blood pH. Carotid ammonium salt infusions characteristically produced acidosis even when alkaline infusates were employed. Frequently there was an early respiratory alkalosis, but acidosis soon predominated.

In 30 experiments utilizing such an alkaline ammonium infusion, marked acidosis (pH less than 7.3) occurred in 21 cases. In 16 of these experiments the peripheral blood pH was below 7.2, and in 5 other instances below 7.3. In the 4 remaining cases acidemia was slight (pH 7.3 or higher).

In 3 animals coma was produced in the usual fashion with a marked acidemia. Three minutes after the onset of coma a 5 per cent sodium bicarbonate infusion was begun in a peripheral vein and the blood pH was brought to 7.3 to 7.4. Despite this compensation for acidosis the animals remained in coma.

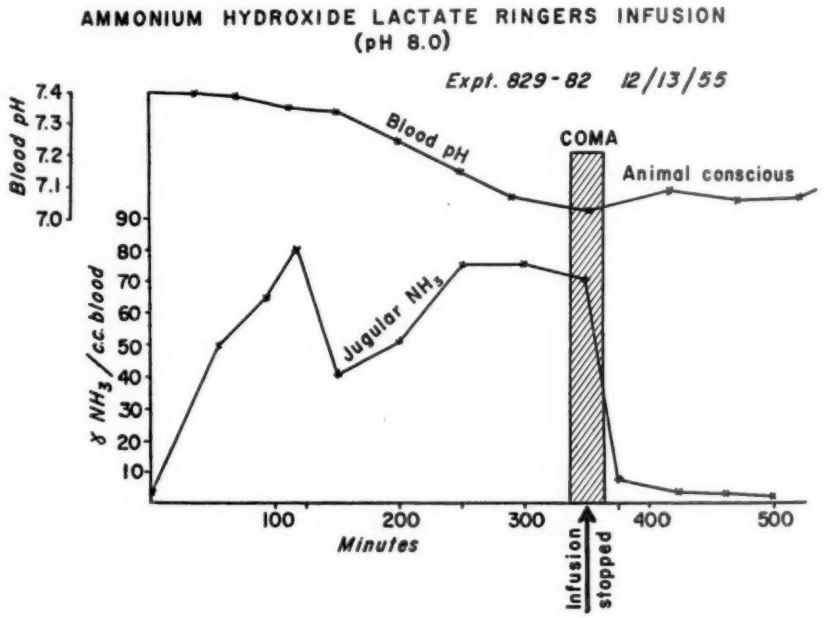


Fig. 5.—Reversibility of coma upon cessation of carotid ammonium infusion. Note persistence of acidosis after ammonium infusion is stopped, ammonia blood levels return to normal, and animal is conscious.

In the 6 experiments where the peripheral venous blood pH was maintained at 7.4 by a separate sodium bicarbonate infusion, coma was produced that was indistinguishable from that produced in the acidotic animals.

There was no correlation ($p = 0.27$) between the blood pH at the time of coma and the length of the ammonium infusion prior to coma. The rate of development of coma was positively correlated ($p < 0.001$) with time required for fall of peripheral blood pH to 7.2. Similarly, coma appeared more quickly following the initial rise in peripheral blood ammonia concentration in the more acidotic animals ($p < 0.01$). These relationships would suggest that acidosis either contributes to or results from coma produced in this fashion.

The animals characteristically showed an increased respiratory rate throughout the infusion (Fig. 4, *A*), but occasionally the respiratory rate decreased (Fig. 4, *B*). In both instances both acidosis and coma ultimately supervened, suggesting that the respiratory rate is not of primary importance.

During the first hour of the infusion a respiratory alkalosis of mild proportions frequently was observed but coma did not appear at this time. Such alkalosis was soon followed by acidosis which dominated the clinical and blood biochemical picture up to and throughout coma. Only by the addition of a separate bicarbonate infusion could this acidosis be overcome.

4. Four experiments, of which Fig. 5 is an example, were performed to determine whether ammonia induced coma in dogs is reversible. In each case after the ammonia infusion was stopped, the ammonia blood levels decreased within a few minutes toward normal and the dogs awoke and soon showed no neurologic abnormalities. Acidosis characteristically persisted for 3 to 6 hours, thus furnishing added evidence that pH variations are but a minor factor in the production of coma due to ammonia toxicity.

Cerebral edema as the cause of coma was excluded by determination of the water content of the brain. As shown in Table III, there was no significant difference between the treated and control animals.

TABLE III. PER CENT HYDRATION OF BRAINS OF AMMONIUM SALT-INFUSED DOGS COMPARED TO 5 PER CENT GLUCOSE IN WATER-INFUSED CONTROLS

NORMAL		TREATED	
PER CENT HYDRATION	STANDARD DEVIATION	PER CENT HYDRATION	STANDARD DEVIATION
73.00	0.18	72.1	0.13
73.60	0.42	72.0	0.03
73.6	0.42	71.8	0.17
72.6	0.58		
73.1	0.08		

Histologic study of the brain* in 7 animals failed to show the microscopic lesion that is said[1] to be characteristic of hepatic coma.

DISCUSSION

Coma was uniformly produced in every animal in which ammonium salts were infused into the carotid artery, regardless of the pH of the infusate, the pH of the peripheral venous blood, or the nature of the ammonium salt. Furthermore, the coma disappeared when the ammonium salt infusion was stopped and the peripheral blood ammonium concentration returned to normal, even though acidosis persisted for some hours. All of this evidence offers direct support to the hypothesis that ammonia per se is capable of producing neurologic abnormalities and coma.

There was no direct relationship between the jugular blood ammonia concentration at the time of coma and the appearance of unconsciousness. In order to precipitate relatively rapid onset of coma and to obtain measurable and significant tissue biochemical changes, infusions of ammonia-producing blood

*Kindly performed by Dr. John Denst, Department of Pathology, University of Colorado School of Medicine.

concentrations far beyond the range found in hepatic disease were employed. Even with such high concentrations in the arterial blood unilaterally perfusing the brain, coma did not immediately ensue and did not appear until after the peripheral blood ammonia concentrations became elevated. Apparently elevation of blood ammonia concentration in both carotid arteries is necessary for the production of coma. Under the experimental conditions such bilateral elevation occurred only after several hours of ammonia infusion, when the ability of the liver to maintain a normal blood ammonia concentration was exceeded.

The time required for the production of coma varied markedly (50 to 520 minutes) in these experiments, a fact apparently related not only to the type of carotid infusate and subsequent venous blood pH, but also to the difficulty in maintaining a constant rate of intra-arterial infusion.

Coma caused by ammonia intoxication does not depend primarily either upon alkalosis or acidosis, for, as has been shown, it could be produced regardless of the peripheral blood pH. Typically, an early alkalosis was followed by a more profound acidosis which persisted throughout coma. It is possible that such an acidosis results from lactic acid accumulation and loss of fixed base occurring after suppression of the oxidative phase of glucose metabolism. Such a change has been postulated by Bessman[2] to be the result of the intracellular combination of ammonia with alphaketo glutamate.

The early transient alkalosis often observed during the first 30 to 60 minutes of our experiments was routinely accompanied by an increased respiratory rate, which is in keeping with the observations of Vanamee,[9] Roberts,[8] Lawrence and Randall,[7] and their co-workers. They have found that respiratory alkalosis predominates and believe it is of primary importance in experimental ammonia intoxication and in clinical hepatic coma.

Under the conditions of our experiments which differ markedly from those of Randall and Roberts and associates, acidosis, not alkalosis, predominates and the significance of blood pH change in the production of coma is questioned. The differences noted might be resolved by assuming that ammonia gas crosses the blood brain barrier during alkalosis in the initial part of the experiment, but thereafter oxidative carbohydrate metabolism is suppressed and an overwhelming metabolic acidosis ensues. Under the experimental conditions here employed, sufficiently large amounts of ammonia were infused to provide continued blood brain ammonia transfer despite an acid pH.

CONCLUSIONS

1. The infusion of various ammonium salts into the carotid circulation of dogs invariably produces coma regardless of the subsequent blood pH alteration. Characteristically under these experimental conditions, there is an early respiratory alkalosis followed by an acidosis that persists throughout the period of coma.

2. Coma due to ammonia intoxication is promptly reversed by termination of ammonia infusion, even though acidosis may persist.

3. Such coma appears only after prolonged (50 to 520 minutes) elevation of the jugular blood ammonia concentration far in excess of that found in liver disease, but shortly (less than 60 minutes) after a rise in femoral venous blood ammonia concentration. This suggests that bilateral carotid arterial ammonia elevation is a prerequisite for the production of coma.

4. Ammonia itself is responsible for coma under the experimental conditions described and does not depend in a major degree upon any particular alteration in blood pH.

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FACTORS PREDISPOSING TO SPONTANEOUS PERFORATION OF THE ESOPHAGUS

The Mechanical Strength of the Ulcerated Esophagus

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As usually defined, rupture of the esophagus refers to a tear in an undiseased esophagus, whereas perforation signifies an erosion of the wall, except when produced by external trauma or instrumentation. This study was designed to test a series of fresh autopsy specimens in an effort to define the importance of the mucosa in maintaining the integrity of the esophagus, for clinical experience indicates that the syndrome of spontaneous perforation results from a combination of 2 processes—mucosal ulceration followed by rupture from vomiting.

METHODS

This has been a study at 10 autopsies, performed immediately after the patient's death. With the esophagus in situ, the stomach was opened to permit the lower esophageal mucosa to be stripped away. An occluding clamp was then placed across the stomach 3 to 4 cm. below the esophagus. A catheter was introduced through the mouth into the upper esophagus to permit the introduction of air and the measurement of intraesophageal pressure. The catheter was fixed in position and the esophagus rendered airtight by placing a ligature around the upper thoracic esophagus. Graduated, slowly increasing pneumatic pressure was then applied via the catheter.

RESULTS

As the intraluminal pressure was increased, 4 of the 10 esophagi suddenly burst, with air quickly dissecting along the periesophageal tissues into the base of the neck and throughout the mediastinum. The remaining 6 specimens developed a slowly progressive leak, with the air initially in the lower periesophageal region, but as the pressure was increased the air progressively dissected cephalad, as well as throughout the mediastinum.

The disruptive pressure varied from 1.0 to 2.25 pounds of pneumatic pressure per square inch; the average was 1.8 pounds per square inch.

Confirming the extensive studies of others, 3 additional esophagi were tested with the mucosa intact. The disruptive pressure in these 3 was found to be 3.8, 5.7, and 6.3 pounds per square inch, respectively.

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DISCUSSION

The esophagus has no serosal covering and very little adjacent support in the lower portion. Its musculature is peculiar in that its upper third is striated, the middle third is an intermingling of striated and smooth fibers, and the lower third is smooth muscle. Immediately above the esophagogastric junction, the fibers of muscle fan out to form a broad coating to the stomach, thereby diluting the musculature of the lower esophagus. The mucosa, the strongest layer of the esophagus, receives little support from the thin interlacing fibers of the submucosa.

Mackler,[18] duplicating the work of MacKenzie[17] and Burt,[3] demonstrated that the pressure required to rupture a freshly removed esophagus ranged from 4.5 to 7.4 pounds per square inch, with an average of 5 pounds. These findings differed from those of Andrews[1] who found the average disruptive pressure to be 7.5 pounds per square inch; however, their modes of experimentation were different. Mackler used the entire esophagus whereas Andrews used only segments. Kinsella and associates[15] determined the bursting pressure of the esophagus on fresh human cadavers and found the range to be between 1.9 and 6.3 pounds per inch, with an average of 3.7 pounds. They described all the perforations of the esophagus as being longitudinal tears of the distal one-third. In all parts of the gastrointestinal tract, Burt[3] found that the mucosa was invariably the last layer to rupture. He noted that in both adults and children the various parts of the gastrointestinal tract ruptured at approximately the same pneumatic pressure; slightly higher pressures were required in children. Andrews[1] credited Senn with the observation that bowel which had been weakened by enteritis ruptured at a pressure of only 1.5 pounds per square inch. In all experiments such as these the dominant factor in the perforation of the alimentary tract is the rapidity with which the intraluminal pressure is increased, rather than the degree of pressure per se.

Using an electromagnetic transducer to record esophageal pressures during swallowing, Butin and associates[4] described an average pressure of 63.6 cm. of water in the lower esophagus and 66 cm. of water in the midesophagus, pressures roughly equivalent to 1.0 pound per square inch.

Drye[8] recorded the intraperitoneal pressure in 9 humans. He described an average rise from 8 cm. of water to 150 cm. (2.2 pounds per square inch) of water with coughing, 80 cm. of water (1.2 pounds per square inch) with retching, and 40 cm. of water (0.6 pound per square inch) with defecation. If the intraperitoneal pressure reflects the intraesophageal pressure, coughing and vomiting may result in a sudden rise in the intraluminal pressure which, in the presence of esophageal disease, may prove critical.

Mallory and Weiss[19] occluded the pylorus and constricted the esophagus. They then partially filled the stomach and found that if the stomach was forcefully compressed, a vertical linear tear was produced in the lower esophagus. They postulated that perforation of the esophagus was due primarily to a mechanical factor. Such an occurrence was reported by Kerr and associates.[14] Their patient, a 3-year-old boy, bit an innertube which was bulging through a

tractor tire. This resulted in a rupture of the esophagus in an area similar to that seen in postemetic rupture. As in the experimental tears, the child's rupture occurred in a longitudinal direction.

While perforation of the esophagus may be produced by mechanical factors alone, local esophagitis and ulceration may weaken the esophageal wall and predispose it to rupture. In routine post-mortem examinations, the incidence of esophagitis has been found as high as 7 per cent,[5] the incidence of acute ulceration of the esophagus is equal to that of the stomach.[25] Contact of acid gastric juice with the esophageal mucosa, whether brought about by vomiting or by direct application, has a prompt and devastating effect upon the mucosa.[10] Esophageal ulceration has been reported in association with a faulty esophagogastric sphincteric mechanism which allows reflux of gastric contents[5] in association with mid-brain lesions[6, 12, 23] or in association with the alarm reaction.[7, 11, 21, 24]

Spontaneous perforation of the esophagus has been reported primarily in association with disease of the central nervous system,[9] pyloric obstruction,[2] or chronic vomiting from any cause.[13, 16, 20, 22] Derrick, Wilkinson, and Howard[7] recently reported the death of 2 children with severe thermal burns; death occurred within 22 hours of a perforated lower esophagus secondary to acute esophageal ulceration and vomiting.

SUMMARY

The bursting strength of the intact human esophagus is approximately 3.0 to 7.5 pounds per square inch. Removal of its mucosa reduces this critical pressure to 1.0 to 2.25 pounds per square inch. Acute ulceration of the esophageal mucosa might therefore weaken the wall to such an extent as to predispose it to rupture following even so minor a mechanical stress as vomiting.

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ISCHEMIC NECROSIS OF THE GASTRIC REMNANT

An Uncommon Complication of Radical Subtotal Gastrectomy

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IT has been observed clinically that a small cuff of fundic tissue serves to prevent or minimize the metabolic disability induced by total gastrectomy.[20] This observation, coupled with the obviously abundant vascularity of the stomach, has led to more extensive gastric resections in the treatment of carcinoma and juxtaesophageal gastric ulcers.

The need for caution in the extent of proximal devascularization of the stomach was demonstrated by Rutter,[22] who in 1953 reported a case of ischemic necrosis of the gastric pouch following subtotal gastrectomy. Spencer[25] described a similar case with 6 others obtained by personal inquiry. Stuart and Jordan[26] reported a case of infarction of the gastric remnant and one other obtained by personal communication, bringing the number of recorded cases to 10. Undoubtedly other unreported or unrecognized cases have occurred.

The gravity of this complication is evidenced by the fact that survival has been reported in but 2 patients, one of whom required excision of the remaining stomach. The purpose of this communication is to report 2 more cases of ischemic necrosis of the gastric pouch with one surviving patient in whom total gastrectomy was not required and to discuss means of preventing, recognizing, and treating this unusual complication of gastric resection.

CASE REPORT

Case 1.—F. M., a 57-year-old white man, was admitted to Montefiore Hospital for the fourth time Nov. 8, 1956, complaining of severe epigastric pain of 3 weeks' duration. He had noted upper abdominal pain for 16 years, and laparotomies performed in 1940 and 1947 at other hospitals revealed no pathology. Gastrointestinal series, barium enema, and oral cholecystography performed in 1953 at this hospital were not remarkable. The patient was a severe asthmatic and was considered to be psychoneurotic. His weight decreased from 110 to 92 pounds in the year prior to admission.

Physical examination disclosed a poorly nourished man with emphysema and epigastric pain and tenderness.

Laboratory data revealed a hematocrit of 47 per cent, occult blood in the stool, and achlorhydria to histamine on gastric analysis. A gastrointestinal series demonstrated a large lesser curvature gastric ulcer midway between the fundus and the antrum, thought to be benign. Gastroscopy was performed; the endoscopist's impression was that the patient had an ulcerating carcinoma of the stomach.

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Laparotomy was performed on Nov. 27, 1956. A mass involving the mid-portion of the body of the stomach was noted, with inflammatory adhesions to the pancreas. A radical subtotal gastrectomy with en bloc omentectomy and splenectomy was performed. The left gastric artery was divided just distal to its origin, and an antecolic Polya anastomosis was constructed with the afferent jejunal limb at the greater curvature of the gastric pouch. Approximately 90 per cent of the stomach was resected without the use of clamps. Although no change in the color of the gastric remnant was noted, bleeding from the cut end was less than usual. The splenic bed was drained through a left upper quadrant stab wound, and the patient was sent to the Recovery Suite in good condition. Pathologic examination of the specimen revealed a benign gastric ulcer.

On the first postoperative day a tracheostomy was performed because the patient was having difficulty in managing his respiratory secretions. Small oral feedings given on the following day were well tolerated, and by the fourth postoperative day he was taking 6 feedings and having bowel movements. The patient's temperature was maintained at 102° F. Inspection of the wound disclosed no abnormalities.

Still febrile, although in good general condition, he complained of left subcostal pain 2 days later. Subphrenic abscess was suspected and barium swallow with fluoroscopy of the diaphragm was performed (Fig. 1). This disclosed good function of the anastomosis, no increase in retrogastric space, and adequate excursion of the diaphragmatic leaflets. On the ninth postoperative day bile-stained fluid appeared at the drain site, and the presence of a fistula was confirmed by giving carmine red by mouth.

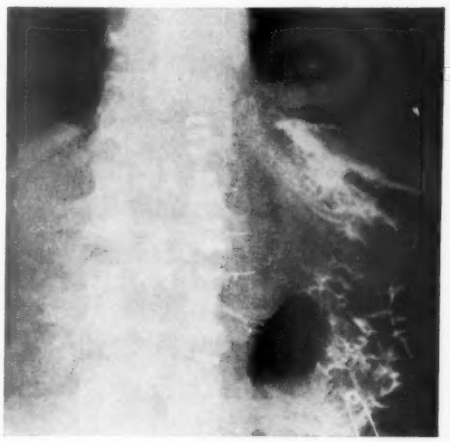

Fig. 1.—Case 1. Barium swallow 6 days following gastric resection. There is no evidence of a leak from the small gastric pouch.

Re-exploration was performed that day through the original incision. A dye-stained patch, 3 cm. in diameter, was noted along the greater curvature of the gastric pouch just above the anastomosis. The suture line appeared intact. Methylene blue instilled through the Levin tube leaked through this area, which had the consistency of wet blotting paper, and through the suture line. Attempts to invert the necrotic area by sutures proved unsatisfactory. Instead, a wedge of the greater curvature of the gastric pouch including the necrotic area was excised, together with a portion of the attached afferent jejunal limb. The defect in the remaining gastric pouch and efferent jejunum was closed. The proximal jejunum was trimmed to within 2 inches of the ligament of Treitz and anastomosed end-to-side to the distal jejunum. In this manner, a Roux Y gastrojejunostomy was constructed (Fig. 2). The patient tolerated the procedure well. Pathologic examination of the segment of stomach and attached small bowel revealed a necrotic area of gastric wall with a pinpoint perforation just above an intact anastomosis. The gastric mucosa was hemorrhagic and necrotic and there was thrombosis of submucosal vessels.

The patient was taking oral feedings by the third postoperative day. He developed a pneumonitis following a trial without the tracheostomy on the twelfth postoperative day. Pulmonary insufficiency delayed decannulation. He was discharged on Jan. 25, 1957, 50 days after the second operation. When seen in the Surgical Outpatient Clinic on Feb. 28, 1957, he had gained 8 pounds, although he had a mild dumping syndrome. Barium swallow revealed some increase in the size of the gastric pouch (Fig. 3).

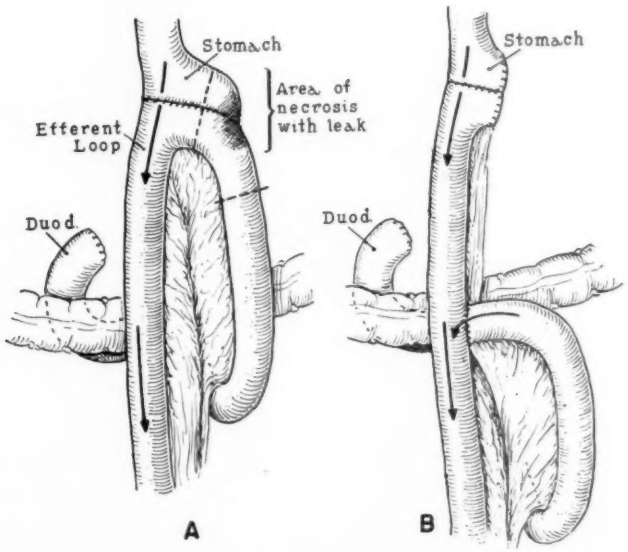

Fig. 2.—Case 1. Re-exploration on the ninth postoperative day revealed necrosis of the greater curvature of the gastric remnant. This area was resected and Roux Y gastrojejunostomy was performed.

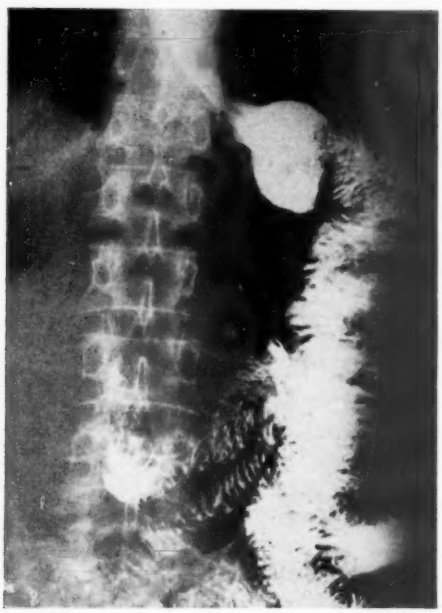

Fig. 3.—Case 1. Barium swallow 4 months following the second operation. There has been an increase in the size of the gastric remnant.

CASE 2.—M. M., a 53-year-old white woman, was admitted to Montefiore Hospital because of anemia and upper abdominal pain of one year's duration and intermittent fever of one month's duration. On physical examination the liver was palpable one fingerbreadth and the spleen 2 fingerbreadths below the costal arch.

Laboratory findings were a hemoglobin of 9.8 Gm., and leukocyte count of 3,000 per cubic millimeter with a normal differential. Radiographic examination of the gastrointestinal tract showed a mass involving the greater curvature of the stomach consistent with a lymphoma.

Laparotomy was performed on Feb. 11, 1957. A mass involving most of the greater curvature of the stomach was noted. The liver and spleen were enlarged but did not appear abnormal. A radical subtotal gastrectomy with omentectomy and splenectomy was performed. Approximately 90 per cent of the stomach was resected, with the use of the Von Petz clamp. An antecolic Hofmeister gastrojejunostomy was constructed, and distal to this, a side-to-side jejunojejunostomy and a feeding jejunostomy. The gastric remnant appeared cyanotic, and there was concern regarding its viability. Its color improved, however, following the removal of some sutures constricting the closed lesser curvature. The liver was biopsied and the splenic bed drained through a left upper quadrant stab wound. The patient tolerated the procedure well. Pathologic examination of the ulcerating gastric tumor revealed retriculum cell sarcoma with involvement of the perigastric lymph nodes. The spleen and liver biopsy were not remarkable.

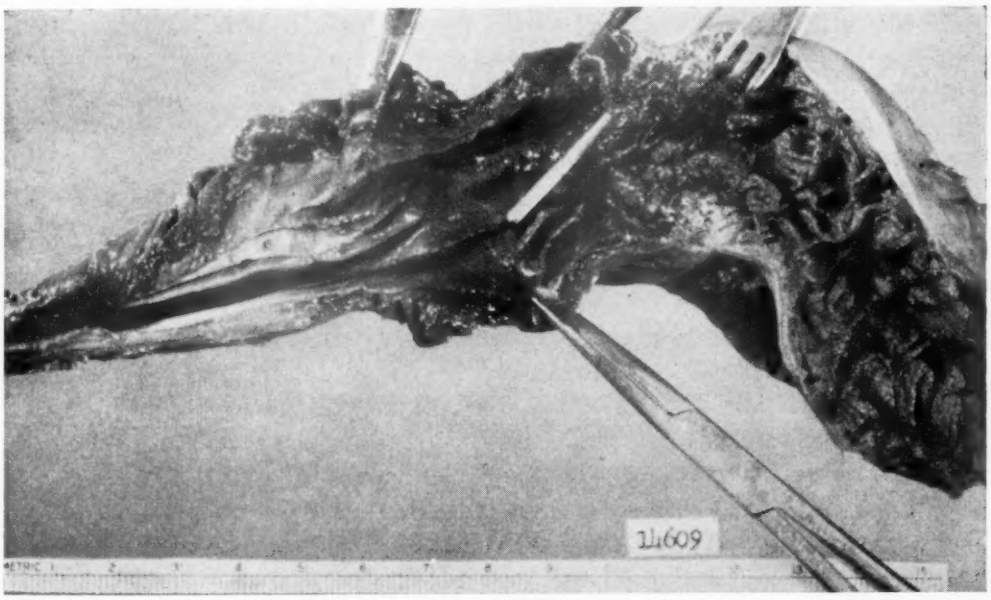

Fig. 4.—Case 2. Autopsy specimen of the esophagus and gastrojejunostomy. There is hemorrhagic infarction of the entire gastric remnant. A probe is passed through the site of perforation proximal to the anastomosis.

On the evening of the operation, the patient's temperature rose to 104.4° F. The day following operation, she was in shock, with a pulse rate of 130 per minute, blood pressure of 60 mm. Hg, and temperature of 104° F. A blood volume study was within normal limits. It was not possible to maintain the patient's blood pressure with pressor agents. On the second postoperative day the patient was icteric, oliguric, and exhibited marked abdominal tenderness with generalized rebound tenderness. The temperature was 103° F.

Disruption of the anastomosis was considered likely. The patient was in extremely poor condition, and it did not appear that she would withstand reoperation. On the fourth postoperative day, bile-stained fluid appeared at the drain site. The patient's temperature

rose to 107° F. and she expired that evening. Post-mortem examination showed hemorrhagic infarction of the entire gastric remnant with perforation of the greater curvature above the suture line, which was intact (Fig. 4).

DISCUSSION

Studies of the blood supply of the human stomach have demonstrated an extensive submucosal plexus, freely communicating mucosal vessels, and absence of end-arteries.[3, 8] Further evidence for the abundant vascularity of the stomach is the rarity of infarction of the intact stomach. Total or partial gastric infarction has been described in cases of occlusion of the celiac axis or its branches with associated severe congestive heart failure.[10] Partial gastric infarction has been described following thrombosis of the coronary vein.[21]

Berman[5] ligated the hepatic, left gastric, and splenic arteries in the treatment of portal cirrhosis; the absence of gastric infarction in these cases is undoubtedly due to the extensive collateral which develops secondary to portal hypertension. Blalock and Levy[7] demonstrated that, in dogs, the development of collateral circulation prevents visceral damage following gradual complete occlusion of the celiac axis and the superior and inferior mesenteric arteries.

Somervell[24] treated duodenal ulcers by extensive devascularization of the stomach and posterior gastroenterostomy. He ligated most of the vessels on both curvatures of the stomach and did not note gastric infarction. That subtotal devascularization of the intact human stomach has little effect on acid secretion is evidenced by the report of Wood.[30] He performed the Somervell operation with poor results, noting marginal ulceration and return of free acid to normal levels. Incomplete devascularization of the stomach in dogs also has no effect on acid secretion and does not prevent the production of Mann-Williamson or histamine ulcers.[1, 4, 14-16]

Various factors are responsible for the trend toward more radical resections of the stomach. Among these are the high incidence of residual carcinoma reported in the gastric remnant,[19] dissatisfaction with the Madlener procedure for juxtaesophageal gastric ulcer,[13] and efforts to reduce the incidence of marginal ulcer.

Maingot,[17] when performing gastric resection for carcinoma, ligates the left gastric artery at its origin and its esophageal branch close to the right border of the esophagus, dividing most of the gastrosplenic omentum. The tubular gastric remnant has "attenuated vascular connections with the spleen." Hinton and Localio[13] construct a tube of the greater curvature after securing all the vasa brevia and resecting the lesser curvature to the esophagus. Visick[28] usually preserves one of the vasa brevia but occasionally divides all of them to leave "a small devascularized remnant" of stomach. Wangensteen[29] has described instances of leaving a 5 per cent gastric pouch devoid of any blood supply except from the esophagus. Ischemic necrosis of the gastric remnant was not noted by these authors.

The risk of embrarassing the blood supply to the gastric remnant has received little attention in the past. Barber[2] reported that gangrene of the proximal gastric segment could occur after segmental gastrectomy and in patients

with poor circulation. Smith[23] noted that the frequency of impaired blood supply to the proximal stomach is in direct relationship to the level of resection and suggested preservation of the blood supply on the greater curvature. Commenting on Visick's "measured radical gastrectomy," McEvedy[18] warned against extensive devascularization of the gastric pouch, stating that "necrosis of mucous membrane and even sloughing of the posterior wall of the stomach have been known to follow." A clear-cut warning in this regard is the statement of Cutler and Zollinger[11] that "if the left gastric artery has been ligated proximal to its bifurcation and the spleen has been removed, the blood supply to the stomach has been so compromised that the surgeon is committed to total gastrectomy."

There is ample experimental evidence to support this statement. Bernheim[6] demonstrated that in dogs the stomach can withstand any amount of diminution of blood supply short of total devascularization. Layne and Bergh,[15] Babkin and his associates,[1] and Le Veen[16] also produced infarction of the stomach by ligating its 4 major arteries. In these studies, the proximal greater curvature was the area most frequently infarcted. Cate and Dawson[9] noted that the incidence of infarction of the gastric pouch in dogs subjected to radical subtotal gastrectomy, omentectomy, and splenectomy was directly proportional to the size of the remnant. When this procedure was combined with mobilization of the cardioesophageal junction, there was an increased incidence of necrosis of the residual pouch, despite its smaller size. These authors stressed the importance of the inferior phrenic artery as a means of vascularizing the proximal gastric pouch and noted that the largest collaterals were present along the lesser curvature.

The relative immunity of the human gastric remnant to ischemic necrosis following similar operative procedures may be related to the origin and size of the left inferior phrenic artery and the esophageal branches of the left gastric artery. Swigert and co-workers[27] studied the arterial blood supply to the abdominal esophagus in 150 specimens. In 94.7 per cent of cases, the left gastric artery had 1 to 3 esophageal branches, anastomosing with branches of the left inferior phrenic artery.

The right and left inferior phrenic arteries are highly variable in their origin.[12] They most commonly arise, either by a common trunk or independently, from the aorta or celiac axis; one may arise from the aorta or celiac artery and the other from the left gastric or renal arteries. In 56 per cent of Swigert's cases the left inferior phrenic artery supplied the esophagus. In all but 8 per cent of these cases there was a single branch. The right inferior phrenic artery furnished an esophageal branch in only 3.3 per cent of cases.[27]

It would appear that an anatomic situation most favorable to infarction of the gastric pouch exists when the left inferior phrenic artery originates from the left gastric artery, as it does in 2.6 per cent of cases.[12] If the left gastric artery is ligated proximal to its phrenic and esophageal branches, the gastric remnant would be weakly vascularized via the thoracic esophageal arteries, and gangrene is likely to occur.

TABLE I

AUTHOR	CLINICAL DATA	EXTENT OF DEVASCULARIZATION	SPLENECTOMY	DRAIN EMPLOYED	ANASTOMOSIS	FISTULA NOTED	FINDINGS AT EXPLORATION, TREATMENT	RESULT
Rutter, 1953	(1) 40 year-old man; gastric ulcer near cardia	Left gastric artery ligated near its origin, greater curvature "extensively mobilized"; gastric remnant not abnormal	No	Yes	Billroth I	5 days postop.	Necrosis of entire remnant; small lesser curvature perforation, large greater curvature perforation; jejunostomy	Died 11 days postop.
Spencer, 1956	(2) 54-year-old Negro woman; gastric carcinoma	Left gastric artery ligated at its origin; gastric remnant appeared mottled	Yes	Yes	Antecolic Hofmeister	36 hours postop.	Gangrene of greater curvature; total gastrectomy, Roux Y gastrojejunostomy	Survival
Spencer, by personal inquiry	*(3) 60-year-old man; gastric carcinoma	All but 2 inches of greater curvature resected; gastric remnant of normal color	Yes	Yes	Antecolic Polya	3 days postop.	Not reoperated	Died
	†(4) 49-year-old woman; gastric carcinoma and carcinoid	Left gastric artery ligated at origin; gastric remnant appeared dusky	Yes	Yes	Segmental gastric resection	5 days postop.	Jejunostomy	Died
	†(5) 35-year-old man; pyloric ulcer	Left gastric artery ligated at origin; gastric remnant of normal color	Yes	Yes	Not stated	5 days postop.	Partial necrosis of stomach near esophagus, treated by plication	Survival
	*(6) No data		Yes	?	Not stated			Died

	(7) No data		Yes	?	Not stated			?
	(8) No data		No	?	Not stated			?
Stuart and Jordan, 1957	(9) 61-year-old man; bleeding gastric ulcer near esophagus	Not stated	No	No	Billroth I	8 days postop.	Necrosis of entire remnant, left subphrenic abscess, total gastrectomy, Roux Y esophagojejunostomy	Died
Stuart and Jordan, by personal inquiry	(10) 54-year-old man; high-lying gastric ulcer	Not stated	?	?	Not stated	Not stated	Not stated	?
Fell et al.	(11) 57-year-old man; ulcer of pars media of stomach	Left gastric artery ligated near origin; gastric remnant not abnormal	Yes	Yes	Antecolic Polya	9 days postop.	Area of necrosis, 2 by 3 cm. on greater curvature of stomach above suture line; wedge resection of greater curvature of stomach; Roux Y gastrojejunostomy	Yes
	(12) 53-year-old woman; reticulum cell sarcoma of stomach	Left gastric artery ligated at its origin; gastric remnant appeared cyanotic	Yes	Yes	Antecolic Hofmeister	4 days postop.	Not reoperated; necrosis of gastric remnant noted at autopsy	Died 4 days postop.

*Personal communication from Dr. George Crile, Jr.
†Personal communication from Dr. Julian K. Quattlebaum.

COMMENT

In analyzing the information available in 12 reported cases of ischemic necrosis of the gastric remnant (Table I), certain facts appear significant. The extensive resection of the stomach was necessitated by either carcinoma or juxtaesophageal gastric ulcers. The left gastric artery was ligated at its origin in at least 6 of the 12 cases, and splenectomy was performed in 8. Cyanosis or mottling of the gastric remnant was noted in but 3 instances. Drains were employed in 7 cases. The time of occurrence of the gastric fistula was variable; it ranged between 36 hours and 9 days following operation.

Reoperation was performed in 6 cases. Inversion of the necrotic area by suture was employed in one case with survival of the patient. In 2 instances, total gastrectomy with Roux Y esophagojejunostomy was performed; one of these patients survived. Excision of the necrotic greater curvature of the stomach with Roux Y gastrojejunostomy was performed in one case with survival. Jejunostomy was performed in 2 patients who later died. Thus, survival has been reported in only 3 of the 12 patients who developed ischemic necrosis of the gastric remnant following subtotal gastrectomy.

In view of the clinical, experimental, and anatomic observations previously cited, certain recommendations may be made regarding the technique of radical subtotal gastrectomy and the prevention and diagnosis of necrosis of the gastric remnant. The esophageal branch of the left gastric artery requires division only in cases of juxtaesophageal lesser curvature ulcers. In this situation it is necessary to preserve the upper vasa brevia which supply the vulnerable greater curvature. If splenectomy is to be performed in continuity with the gastric resection, the left gastric artery should be ligated distal to its esophageal branch. Inversion of the lesser curvature portion of the gastric remnant would appear to be undesirable, since it reduces the blood supply to the greater curvature where gangrene is most likely to occur. As Visick[28] has noted, the gastric remnant becomes tubular with mobilization of the greater curvature, A Polya anastomosis may then be performed with a relatively narrow stoma.

The color of the gastric remnant and degree of bleeding from its distal incised margin are best observed if the anastomosis is performed without the use of clamps. The application of a crushing clamp may cause submucosal vascular thrombosis or extension of thrombosis originating in an ulcer bed, thus initiating gangrene in a gastric pouch with a precarious blood supply. If inadequate vascularization of the gastric remnant is suggested by pallor, cyanosis, or sluggish bleeding, total gastrectomy is indicated. Drainage of the splenic bed or the region of the gastrojejunostomy may facilitate the diagnosis of ischemic necrosis of the gastric remnant. Fever, upper abdominal tenderness, and profuse drainage suggest the diagnosis. If dye instilled in the stomach appears at the drain site, immediate exploration is mandatory. Instillation of dye via the Levin tube may be required during surgery since the gastric remnant may not demonstrate an obvious perforation in an area of necrosis. Rather, it may have the consistency of wet blotting paper in the region of the greater curvature; the leakage of dye through the gastric wall will demonstrate the area of necrosis.

It may be possible to treat a small area of gastric necrosis by plication. More extensive infarction of the gastric remnant will require total gastrectomy, unless the original operative procedure allows for resection of the necrotic greater curvature and Roux Y gastrojejunostomy, as performed in Case 1.

SUMMARY AND CONCLUSIONS

1. Ischemic necrosis of the gastric remnant is an uncommon complication of radical subtotal gastrectomy. Two cases are reported, and the literature is reviewed.

2. Inadequate vascularization of the remaining stomach is most likely to occur when the left gastric artery is ligated at its origin and splenectomy is performed. In this situation, the gastric pouch is precariously vascularized by the left inferior phrenic artery. Should this vessel originate from the left gastric artery, the viability of the gastric pouch is compromised.

3. The vascularity of the gastric remnant must be critically evaluated when performing high gastric resection. To insure an adequate blood supply to the remaining stomach, the esophageal branch of the left gastric artery must be preserved when splenectomy is performed. In this situation, inversion of the lesser curvature of the gastric remnant reduces the blood supply to the poorly vascularized greater curvature. If the lesser curvature of the stomach is resected to the cardioesophageal junction, it is essential to preserve the upper vasa brevia.

4. The insertion of drains to the region of the gastrojejunostomy facilitates the diagnosis of infarction of the gastric remnant. Once the presence of a gastric fistula is ascertained, prompt surgical intervention is mandatory.

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MODIFICATION OF HOMOTRANSPLANTATION BY GROWTH IN TISSUE CULTURE

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SINCE a homograft undergoes destruction as the result of an antigen-antibody reaction, in order to obtain permanent survival of a graft it is necessary to interfere with this antigen-antibody response in some fashion. Either the antibody reaction of the host to the antigenic stimulus must be inhibited or the antigenicity of the graft must be altered.

Evidence points toward the existence of antigenic specificity of species, of strains of inbred lines, of individuals, and perhaps of organs.[1] Of greatest practical significance in the surgical application of grafting techniques is the individual specificity which exists within a genetic species. This individual specific antigenicity can be altered in several ways, some proved, some only of theoretical significance at present.

This study was undertaken to re-explore the possibilities of in vitro alteration of tissue antigenicity by growth in tissue culture. Previous work in this field has given some indication that cultivation of tissue in the plasma of the intended recipient may modify its characteristics sufficiently to permit permanent survival of homografts.

Stone, Owings, and Gey[21, 22] cultivated fragments of thyroid and parathyroid glands of dogs for a 2- to 4-week period in a medium containing serum and plasma of the intended recipient. The glandular tissue was then transplanted to the areolar tissue of the axilla or groin of the recipient animal. In the early part of their work, they reported failures in almost 100 trials but were able to demonstrate histologic takes up to 6 months after grafting in 5 of 11 thyroid transplants later in the series. No mention is made of the genetic relationship of these dogs. The authors subsequently extended the work to human patients having glandular deficiencies following surgery but felt that the results in these patients were not conclusive.

More recently, Gaillard has also tried to condition grafts in a new chemical environment by cultivating parathyroid tissue from newborn infants in neutral solution for one week and then gradually adding the plasma and serum of the intended recipient over a 14- to 21-day period until the medium was

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completely replaced by serum of the intended receipient. This human parathyroid tissue was then transplanted to patients evidencing parathyroid deficiency following surgery. Seven of the 30 patients were said to show evidence of clinical improvement following this procedure. In none of the cases was histologic proof of viability obtained.[10]

Although Stone, Owings, Gey,[21, 22] and Gaillard[9] feel that they have been able to successfully homotransplant tissue using this technique, others[17] have had equivocal results. Using similar techniques, attempts have been made to adapt pituitary[13] and pancreatic tissue[19] to a new environment before transplantation. In neither case was any surviving viable tissue able to be identified histologically at the time of re-exploration.

If the individual specific antigens could be modified, as the aforementioned studies suggested, they might no longer evoke an antibody response in the host following transplantation. It was hoped that if this concept was substantiated, the clinical applications of this method could be extended.

Numerous studies[3, 23] have indicated that the age of the donor is important in effecting the probability of a successful "take." The earlier in embryonic development a tissue is obtained, the less of an antibody response it will evoke in the intended recipient and therefore the less its antigenicity.

The "law of deficiency" which states that a graft survives only if a host has a physiologic need for it was based upon a series of studies carried out by Halsted[11] in which he was able to successfully autotransplant parathyroid gland only if a significant degree of pre-existing glandular deficiency was present. In a previous study[5] this factor was not found to be of significance in the survival of autografts of thyroid. In the present investigation, its role in homotransplantation was evaluated.

METHOD OF MODIFICATION OF ANTIGENICITY BY GROWTH IN TISSUE CULTURE

Rabbits from mixed stocks were used as recipients and donors throughout this study. The recipient and donor rabbits were not genetically related. Thyroidectomies were performed under sterile conditions. The thyroid glands were washed in saline, cut into fragments approximately 1 mm. in thickness, embedded in a plasma clot, and placed in Carrel flasks to which were added 2 parts of Tyrode's solution, one part of stock rabbit embryo extract (10 to 14 days old) and 2 parts of rabbit serum. After stock rabbit solution was added to the flasks, they were incubated at 38° C. for a 2-week period. The tissue was then grown for another 2-week period in the serum of the intended recipient instead of in stock serum. The fluid in the flasks was changed twice a week. After one month's growth in tissue culture, the thyroid fragments from one lobe were transplanted under the renal capsule of the adult rabbit in whose serum the tissue had been growing for 2 weeks. One month postoperatively, each surviving rabbit was given 5 microcuries of I^{131} subcutaneously. Twenty-four hours later, the rabbits were sacrificed. I^{131} uptake studies were performed and specimens taken for histologic section.

The techniques of cultivation in tissue culture, of transplantation, and of I^{131} administration in all the groups which follow were identical.

RESULTS

Group A.—The first set of donor rabbits used were adult animals. All the recipient nonrelated rabbits had intact thyroid glands. There were 10 survivors in this group. No pickup of I^{131} was demonstrated in any of the rabbits having homologous thyroid transplants. Grossly, occasional small whitish-gray scarred areas about 1 mm. in size could be seen beneath the renal capsule at the sites where the grafts had been inserted. Sections through the kidney in these areas revealed thickening of the renal capsule. The most consistent finding was a hyaline necrosis of the thyroid fragments with pseudoencapsulation by a wall of fibrous tissue which was infiltrated by round cells in many cases.

Group B.— To the possible modification of antigenicity by growth in tissue culture was added a variation in the age of donor tissue. Since the use of thyroid gland obtained from young donors might tend to improve the results, the age of these rabbits was varied in this group. The first set of donors used in this part of the study were 27- to 29-day-old embryo rabbits (gestation period 31 to 32 days). The glands were removed under a dissecting microscope using sterile technique. The second set of donors were one day of age. The recipients were adult nonrelated rabbits with intact thyroid glands. There were twenty survivors. No pickup of I^{131} was demonstrated in any of these rabbits. The same finding of capsular thickening and hyaline necrosis of glandular remnants was seen on the sections (Figs. 1-4). In one case, a few recognizable follicles filled with vacuolated colloid and lined by flattened epithelium were seen beneath the capsule.

Group C.—Becaue it was thought that glandular deficiency might still favorably affect the outcome of homotransplantation, thyroidectomies were performed in one group of adult rabbits in this study. Thyroid glands obtained from donor rabbits of 3 ages were used, 27- to 29-day-old embryos, 1-day-old rabbits, and adult rabbits. Total thyroidectomies were performed on the adult nonrelated recipient rabbits. Only a small shred of tissue thought to be parathyroid gland was allowed to remain at the time of thyroidectomy. Thus, all of the animals in this group had severe thyroid deficiencies. There were 11 surviving rabbits. No uptake of I^{131} was demonstrated in any of the grafts in surviving rabbits in this series. The gross and microscopic pathologic findings were the same as in Groups A and B.

Group D.—Three groups of control animals were prepared in the following manner:

1. In thyroidectomized rabbits, their own thyroid gland was cut into fragments, grown in their own autologous serum in Carrel flasks for one month, and then re-implanted under their own renal capsule. These controls were prepared to be certain that the tissue culture technique used would produce viable thyroid capable of function after a month outside of the body.

Fig. 1.

Fig. 2.

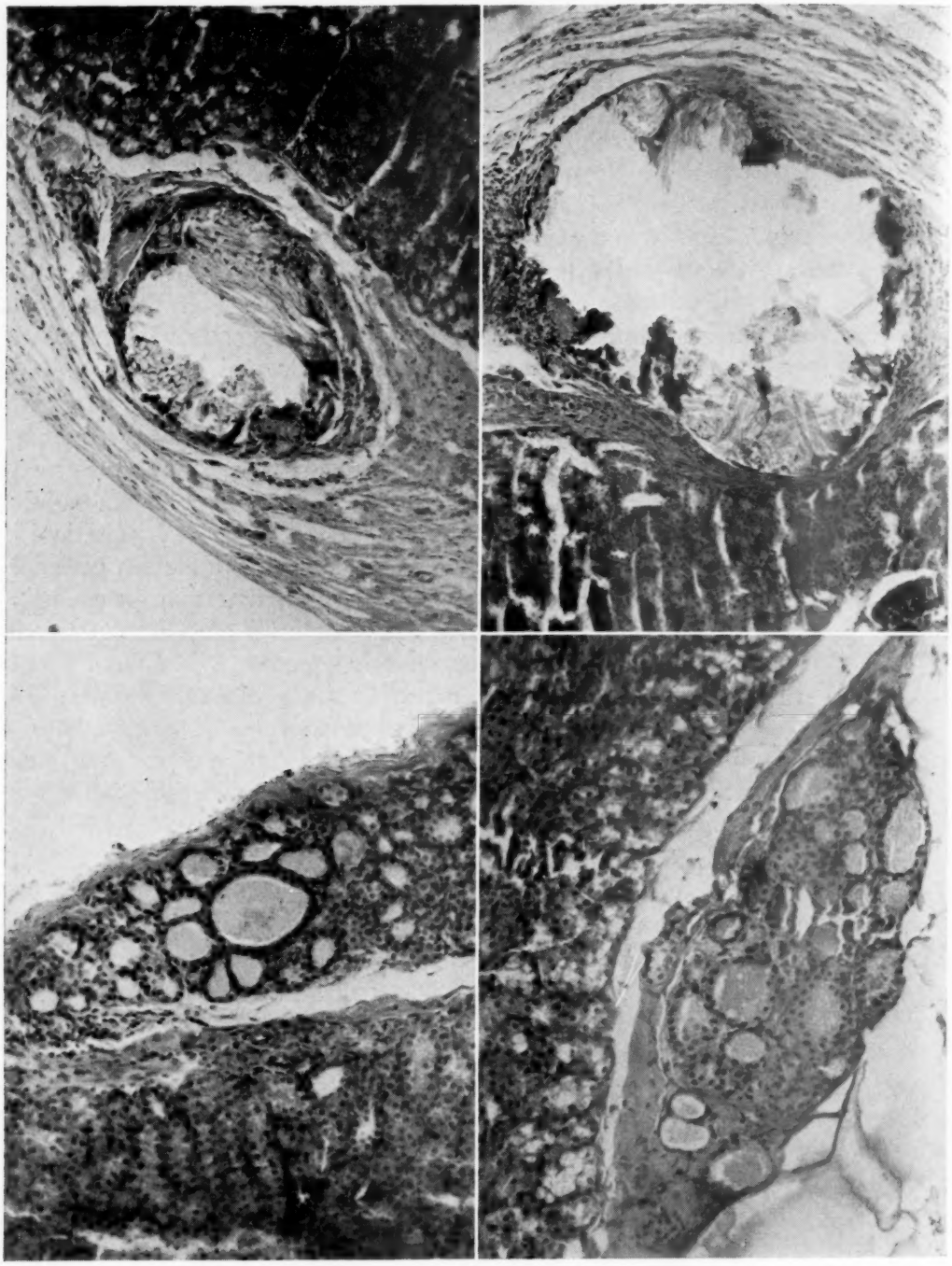

Fig. 3.

Fig. 4.

Fig. 1.—Animal No. 10. Section showing rejection by host of 27- to 29-day-old embryo thyroid gland implanted beneath renal capsule after growth in tissue culture. (×76, 1/11 off reduction.)

Fig. 2.—Animal No. 101. (×70, 1/11 off reduction.) Same as Fig. 1.

Fig. 3.—Animal No. 121. Control. Autotransplantation following growth in tissue culture (×128, 1/11 off reduction).

Fig. 4.—Animal No. 122. Control. Autotransplantation following growth in tissue culture (×130, 1/11 off reduction).

Fig. 5.

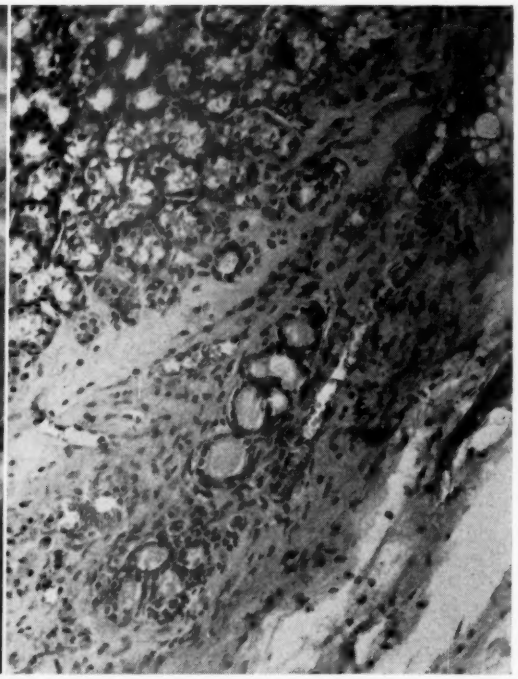

Fig. 6.

Fig. 5.—Animal No. 8. A 27- to 29-day-old embryo thyroid gland. Section showing few recognizable thyroid follicles filled with colloid (×220, 1/11 off reduction).

Fig. 6.—Animal No. 84. Control rabbit. One-day-old thyroid gland grown in stock solution before homotransplantation. A few small thyroid follicles are seen filled with colloid. (×128, 1/11 off reduction).

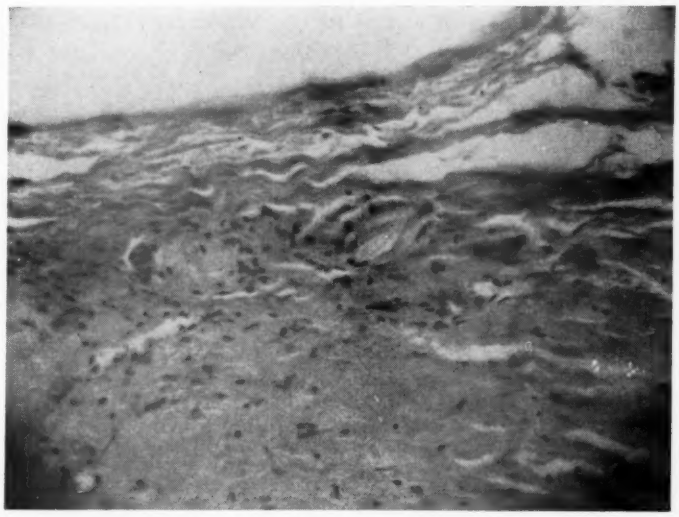

Fig. 7.—Animal No. 128. Control rabbit. Homotransplantation without growth in tissue culture. Demonstrates renal capsular thickening seen as well in many of the sections in this series after growth in tissue culture (×155, 1/11 off reduction).

There was good uptake of I^{131} in 2 of the 3 control rabbits. These glands were thus capable of resuming function after one month in the in vitro environment. In these autotransplanted controls whose thyroid had been grown in tissue culture for one month, viable thyroid gland was visible on section with proliferation of follicles, many of which were filled with colloid.

2. In rabbits with intact thyroids, homologous thyroid gland, after having been grown in stock (rather than specific) serum, was transplanted under the renal capsule.

3. Thyroidectomized rabbits were homotransplanted with fragments of thyroid gland which had not first been grown in tissue culture.

No uptake of I^{131} was demonstrated in the second or third set of controls with homotransplanted thyroid. Capsular thickening and hyalinization of the thyroid remnants as previously described were seen on the sections. In one control rabbit, in Group 2, in which one-day-old thyroid had been transplanted, a few small thyroid follicles filled with colloid were seen. The capsule around them was thickened and no active proliferation of follicular epithelium, apparent in the autotransplanted controls, was seen in this case.

Many of the thyroidectomized rabbits in this experiment developed tetany and died postoperatively. Some of the animals had to be discarded due to contamination of the cultures, thus reducing the final number in the series (Table I).

TABLE I. HOMOTRANSPLANTATION OF THYROID GLAND CULTIVATED IN VITRO

	ADULT DONORS	ONE-DAY-OLD DONORS	27- TO 29-DAY-OLD EMBRYO DONORS
Survivors, no thyroidectomy	10	10	10
Survivors, thyroidectomy	2	4	5
Dead rabbits	4	1	4
Contaminated cultures	1	1	1
Total experiments	17	16	19

It was not possible under the conditions set up in this experiment to favorably influence the success of homotransplants of thyroid by growth in the plasma of the intended recipient. In a few animals, small islands of viable thyroid were seen but in none of the rabbits having homologous thyroid transplants was function demonstrable by uptake of I^{131}. Neither in vitro growth in the serum of the intended recipient for 2 weeks, the use of embryonic tissue, nor glandular deficiency favorably influenced the end-results.

The stimulus to cellular proliferation produced by the hormonal secretions of the anterior pituitary gland will increase the rapidity of cellular growth under propitious circumstances. A viable graft will increase in size more rapidly in vivo or in vitro in the presence of the stimulus of the trophic secretion of the pituitary than in their absence.[17, 23] When a state of glandular deficiency exists, the specific pituitary hormone which stimulates this target gland will be present in higher concentrations than in the normal state. In this manner, a glandular deficiency may favorably affect the growth of a graft. This

does not mean, however, that the original take of the graft is favorably influenced in any way. Nor does it mean that its ultimate survival is significantly prolonged by the presence of increased amounts of the pituitary hormone.

The period of time used for in vitro growth in this study was selected because this period has been reported by previous investigators to give satisfactory results.[10, 21, 22] It is conceivable that with a much longer period of in vitro cultivation, the results might have been different. However, the technical difficulties also increase proportionately and the danger of fibroblastic overgrowth in the culture flasks with diminution of proliferating thyroid epithelium, capable of resuming function when returned to the living animal, is a real one.

In vivo experiments carried out on guinea pigs, while not exactly comparable to this study, give some indication that a longer period of adaptation may be necessary. Woodruff and Woodruff[24] grew thyroid homografts in the avascular anterior chamber of the guinea pig's eye, which, as indicated previously, is in some respects like in vivo tissue culture. In order to determine whether adaptation had occurred, with alteration of antigenicity of the thyroid tissue, they later transferred these viable grafts from the anterior chamber to a subcutaneous site at delayed intervals. These investigators found that no grafts survived if transferred after 28 days or less in the anterior chamber. Six of the 11 grafts transferred after 3 or more months remained viable and continued to survive.

However, more recent evidence would seem to indicate that antigenicity is not lost after even more prolonged periods of cultivation in tissue cultures. In the experiments with actively acquired tolerance,[4] the skin grafts lived for many months in the tolerant recipient animals. However, as soon as the ability to produce specific antibodies was restored by normal lymph node transplants, these grafts sloughed in the expected period of time. No significant adaptation had occurred in this in vivo situation which was certainly a more favorable one than any which could be artificially produced in tissue culture.

Although numerous attempts have been made to transplant tissue, there have only been sporadic investigations suggesting some measure of success. In most of these favorable reports, especially those carried out in man, the effectiveness of the final result has been judged almost exclusively by evidence of clinical improvement but has not included a demonstration of histologic viability of the transplanted tissue. In animals, in a very few studies following endocrine homotransplantation,[7, 15] sections taken at variable periods of time following grafting show what appears to be viable tissue. Stone and Gey show such evidence in their thyroid transplants following growth in tissue culture. Whether this tissue was also capable of functioning cannot be concluded from their study. In 2 of the animals in this present series following homotransplantation of thyroid after growth in tissue culture, islands of surviving thyroid follicles were present which were not capable of concentrating radioactive iodine as did the thyroid autotransplants. It would seem that in order to prove conclusively that homotransplantation has been completely successful it would be necessary to demonstrate not only histologic viability but also function in the same specimen.

SUMMARY

1. In this study, the 3 factors, modification by growth in tissue culture, age of donor, and glandular deficiency were all tested together and separately so that their role in homotransplantation could be better elucidated.

2. Growth of thyroid gland in the serum of the intended recipient in tissue culture following a 2-week period of growth in stock solution did not adapt the tissue sufficiently to produce homograft survival.

3. Use of embryonic thyroid tissue from 27- to 29-day-old fetal rabbits combined with growth of this tissue in the serum of the intended recipient did not favorably influence the results.

4. The presence of a glandular deficiency did not increase the survival or improve the function of grafted tissue following homotransplantation of thyroid gland.

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Calendar of Surgical Meetings

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS. *Annual Meeting,* April 23-25, 1958, Edgewater Gulf Hotel, Edgewater Park, Miss. Secretary-Treasurer, Dr. Wm. J. Engel, 2020 East 93rd Street, Cleveland, Ohio.

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 16-18, 1958, Statler Hotel, Boston, Mass. Secretary, Dr. H. T. Langston, 1919 West Taylor Street, Chicago 12, Ill.

AMERICAN COLLEGE OF SURGEONS. *Sectional Meeting,* March 27-29, 1958, Hotel Fort Des Moines, Des Moines, Iowa.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 19-21, 1958, The Grove Park, Asheville, N. C. Secretary, Dr. Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C.

AMERICAN SURGICAL ASSOCIATION. *Annual Meeting,* April 16-18, 1958, Waldorf-Astoria, New York, N. Y. Secretary, Dr. William A. Altemeier, Cincinnati General Hospital, Cincinnati, Ohio.

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* April 28—May 1, 1958, Roosevelt Hotel, New Orleans, La. Secretary, Dr. Samuel L. Raines, 188 South Bellevue Boulevard, Memphis 4, Tenn.

THE HARVEY CUSHING SOCIETY. *Annual Meeting,* April 21-23, 1958, The Mayflower, Washington, D. C. Secretary, Dr. David L. Reeves, 316 West Junipero Street, Santa Barbara, Calif.

THE INTERNATIONAL CARDIOVASCULAR SOCIETY. *North American Chapter,* June 21, 1958, Sir Francis Drake Hotel, San Francisco, Calif. Secretary, Dr. Henry Haimovici, 105 East 90th Street, New York 28, N. Y.

INTERNATIONAL UNION AGAINST CANCER. *Seventh International Cancer Congress,* July 6-12, 1958, London, England. Secretary General, Harold Dorn, National Institute of Health, Bethesda 14, Md.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 3 and 4, 1958, Mount Washington Hotel, Burton Woods, N. H. Deadline for submission of papers, June 1, 1958. Secretary, Dr. Richard Warren, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 20-22, 1958, Hotel Kahler, Rochester, Minn. Deadline for submission of papers, Sept. 1, 1958. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.

FIBROADENOMA WITH SARCOMA-LIKE STROMA: A BENIGN TUMOR

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THE status of the fibroadenoma with richly cellular, sarcoma-like stroma has varied extensively in the literature of primary breast neoplasms. The present study of the clinical and microscopic features of fibroadenomas with sarcoma-like stroma was undertaken in an attempt to lend some clarification to the confusing picture that currently exists concerning the malignancy or benignity of such lesions. It was felt that consideration of the history and physical findings, gross and microscopic pathology, applied therapy, and clinical course associated with such neoplasms would allow a comprehensive picture with which to evaluate the true nature of these lesions.

MATERIALS AND METHODS

All cases seen at the Mayo Clinic during the 50-year period, 1907 through 1956, in which the term "sarcoma" was used in the diagnosis of a breast neoplasm were selected for study. The histories and operative and pathologic reports of these cases were reviewed and abstracted. The gross and microscopic pathologic features of the available operative specimens were studied and evaluated. In 34 cases the microscopic features of the primary lesions were consistent with a diagnosis of true primary mammary sarcoma. In no lesion considered a primary breast sarcoma was there evidence of a benign epithelial component within the primary tumor mass. All such lesions were excluded from the present study but will be reported in another paper.

In 22 cases microscopic study revealed a benign epithelial component within a primary tumor mass, the stroma of which was richly cellular. The presence of the benign epithelial component indicated to us that the fundamental lesion in these cases was a fibroadenoma. In a single case there was no surgical specimen available for re-evaluation and the diagnosis was based upon permanent sections of the primary tumor made available by the Section of Surgical Pathology.

CLINICAL FINDINGS

The mean age of the 22 patients was 47 years, the extremes being 34 and 68 years. There were 21 women and one man in the series. Thirteen tumors

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Abridgment of a portion of thesis submitted by Dr. Botham to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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were located in the left breast, while only 9 were found in the right breast. The mean duration of the lesion, as recorded in 19 cases, was 50.75 months. In 9 cases a period of rapid growth, averaging 8.1 months, had been recorded. Antecedent trauma was recorded in only one case. Pain in the involved breast had occurred in 12 of the 22 cases, but the detailed character of the pain was unrecorded.

Nipple retraction was noted in a single case, but whether it had been present or not prior to the discovery of the tumor mass was not noted. Fixation of the skin overlying the tumor mass had occurred in 7 cases. Change in color of the overlying skin had also occurred in 7 cases. In no case had ulceration of the overlying integument occurred in spite of the rather large dimensions of many of these lesions. Palpable ipsilateral lymphadenopathy had been demonstrated in 8 of the 22 cases.

Primary surgical therapy had consisted of radical mastectomy (9 cases), radical mastectomy plus roentgen therapy (5 cases), simple mastectomy (4 cases), simple mastectomy plus roentgen therapy (2 cases), simple mastectomy plus axillary dissection plus roentgen therapy (1 case), and local excision (1 case).

In 2 cases recurrent disease ultimately developed. Primary therapy had consisted of local excision in one case and simple mastectomy in the other. In both instances the recurrent disease was amenable to surgical treatment. In the first case simple mastectomy was carried out, while in the second case wide local excision was necessary.

In 13 of the cases in which radical mastectomy had been performed, the surgical specimens were available for gross and microscopic examination. The excised axillary lymph nodes were dissected out and examined grossly. Each lymph node the major part of which was not replaced by fat was sampled for microscopic study. In not one case was any evidence of metastatic tumor tissue detected.

PATHOLOGIC FEATURES

The gross lesions in general were circumscribed, encapsulated, and irregular or bossed on the exterior surface. The size of the lesions was usually large, 15 of them varying from 5 to 15 cm. in one or more dimensions. The smallest lesion was 1.5 cm. in diameter. The tumors were generally quite firm. The cut surface bulged, was smooth and glistening, appeared lobulated, and contained either distended or flattened cystic spaces as well as occasional areas of necrosis. The natural colors of the tumors had been altered by formalin fixation and were therefore not recorded.

The sample blocks of tissue from which the microscopic sections were cut were stained with hematoxylin and eosin.

In each neoplasm the microscopic sections revealed the presence throughout the tumor of a benign epithelial component which existed in the form of distended or flattened cystic spaces or both. Most of the tumor mass in these

lesions was composed of a richly cellular stroma (Figs. 1 and 2). Mitoses were demonstrable in the richly cellular areas within each tumor (Fig. 3). Cellular differentiation, however, was the predominant stromal picture in each of the 22 neoplasms. In no tumor did the richly cellular areas exhibit significant anaplasia or pleomorphism of the stromal cells.

Fig. 1.

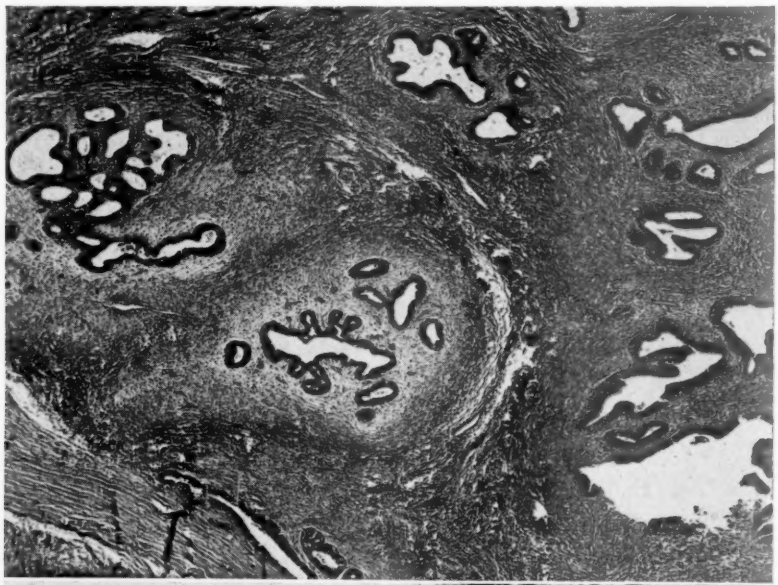

Fig. 2.

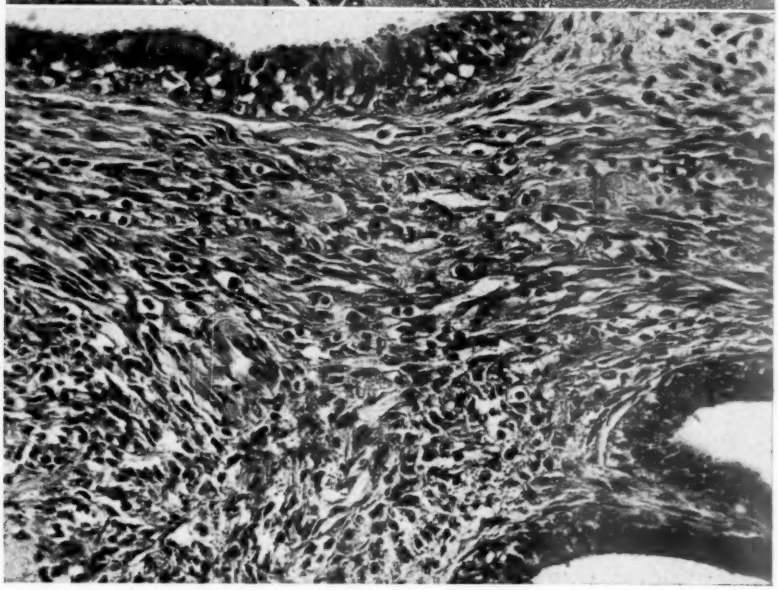

Fig. 1.—Fibroadenoma with richly cellular, sarcoma-like stroma (hematoxylin and eosin; ×30).

Fig. 2.—Sarcoma-like stroma in a fibroadenoma. High-power magnification of the lesion shown in Fig. 1, demonstrating richly cellular stroma with mitosis (hematoxylin and eosin; ×300).

COMMENT

The major problem concerning the fibroadenoma with sarcoma-like stroma has been whether or not it is a benign or a malignant neoplasm. Little doubt can exist regarding the group of histologically malignant, metastasizing, pure mesenchymal breast tumors. A number of authors have included in their classifications of primary breast sarcoma those lesions which contain a benign epithelial component intermixed with richly cellular, sarcoma-like stroma. Such lesions have variously been called "adenosarcoma," "adenofibrosarcoma," and "cystosarcoma phyllodes."

In the earlier literature of primary breast sarcoma 12 to 33 per cent of such lesions contained persistent benign glandular structures.

Bloodgood,[1] while considering such lesions to be breast sarcomas, was aware of a difference in prognosis associated with such lesions and pure breast sarcoma. He had never saved a patient with breast sarcoma other than what had been considered sarcoma in an intracanalicular myxoma.

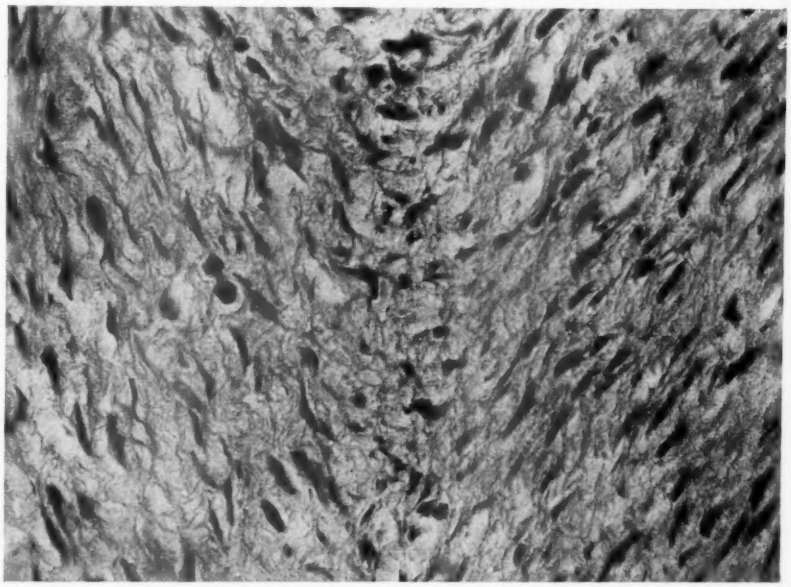

Fig. 3.—Sarcoma-like stroma in a fibroadenoma. High-power magnification of richly cellular area to demonstrate mitosis (hematoxylin and eosin; ×400).

Cheatle and Cutler[2] noted that the connective tissue stroma of a fibroadenoma would occasionally undergo malignant transformation, the microscopic appearance of which was identical with that of sarcoma. They felt that it was the absence of metastasis alone which indicated the essentially benign nature of tumors of this kind.

McDonald and Harrington[5] emphasized that the term "cystosarcoma phyllodes" has been misused to include a whole group of tumors, the great majority of which are benign fibroadenomas. They felt that a small group of undetected fibrosarcomas were responsible for the malignant connotation applied to a group of benign neoplasms.

Hill and Stout[3] felt that the lesions in the literature to which the term "adenofibrosarcoma" had been applied usually manifested a benign course and questioned if they should be called sarcoma at all. They noted that, while the symptoms associated with adenofibrosarcoma and pure fibrosarcoma were practically identical, the clinical course associated with the 2 groups of lesions differed. They recommended local excision as adequate primary therapy for the group of tumors considered adenosarcomas.

Treves and Sunderland[6] considered that cystosarcoma is both a benign and a malignant tumor, a conclusion which seems rather incongruous. Their criterion for diagnosis as a cystosarcoma was "pronounced" overgrowth of the stromal element. They were able to localize the early malignant changes as well as the later definite malignant changes in the stroma of such lesions. To our knowledge, the sarcomatous metamorphosis of a benign to a malignant stroma has never been followed, making the description of what is or is not an early malignant change extremely difficult, if not impossible, to ascertain.

White's case[7] was called a malignant variant of cystosarcoma phyllodes wherein the patient ultimately succumbed with metastasis noted in the opposite breast, anterior mediastinum, and lung. Various pathologists, however, reported this lesion as a carcinosarcoma or adenocarcinoma as well as cystosarcoma. The fact that metastasis of a primary mammary sarcoma to the opposite breast is virtually unknown lends some support to the impression that the primary lesion in White's case may well have been a neoplasm other than sarcoma.

Lester and Stout[4] noted that a tumor may be histologically benign or borderline throughout the majority of its component parts and the malignant portion never be discovered unless multiple sections are taken from all parts of the lesion. One of their lesions classified as histologically benign had metastasized.

It is true that there have been occasional reports of metastasis from so-called adenosarcomas. The metastatic element has always been the mesenchymal tissue and never the epithelial element. It would be extremely interesting to serial section such "metastasizing adenosarcomas" in an attempt to discover whether or not an area of pure anaplastic fibrosarcoma exists within them.

The symptoms, physical signs, and gross pathologic features associated with fibroadenomas with sarcoma-like stroma and true primary mammary sarcoma are extremely similar. However, we have found, as others have, that there is a marked dissimilarity in the clinical course associated with these two types of lesions. The true primary mammary sarcomas are capable of metastasizing and often do metastasize, while their benign counterparts containing an epithelial element rarely, if ever, metastasize.

The lack of demonstrable evidence of metastasis in the 22 cases presented herein corroborates an impression of an associated benign clinical course. The recurrence of a primary neoplasm, as in 2 cases reported herein, may reflect incomplete excision of the primary tumor, with residual neoplasm as the source of the recurrent tumor. That so-called recurrent disease may be a new primary tumor developing in predisposed or potentially neoplastic tissue cannot be refuted but seems rather unlikely. Recurrence of a primary tumor, however,

does not seem significant evidence on which to base an impression of potential or true malignancy. Demonstration of actual metastasis, on the other hand, is irrefutable evidence of a truly malignant tumor.

We are in complete agreement with the many investigators who feel that a fibroadenoma with sarcoma-like stroma is a benign lesion.

Application of the term "cystosarcoma" to such lesions as those presented herein seems inappropriate and unwarranted with the realization that such lesions are not true sarcomas.

Simple mastectomy is an adequate primary surgical procedure for fibroadenomas with sarcoma-like stroma. Wide local excision is indicated in the surgical management of recurrent lesions unless the extent of the recurrence or the condition of the patient precludes further operation.

SUMMARY

On the basis of data on 22 cases of fibroadenoma with sarcoma-like stroma it is concluded (1) that this is a benign lesion which rarely, if ever, metastasizes; (2) that it is capable of recurrence and not infrequently does recur; (3) that simple mastectomy is indicated as primary surgical therapy for such lesions; and (4) that wide local excision is indicated in the surgical management of recurrent lesions.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

SUCCESSFUL MARROW HOMOGRAFT IN THE DOG AFTER RADIATION

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INTRODUCTION

EFFORTS to secure lifesaving homografts of marrow after lethal total body radiation in the dog have in general been disappointing.[1,5] In fact, no clear instance of demonstrated success seems to have appeared in the literature. This is unfortunate since success with bone marrow would presuppose success with other subsequent homografts in a species well adapted to experimental surgical procedures.

Our first thought was that possibly the usual 250 kv. single source of radiation was not adequate to secure the uniform radiation effects potentially needed for successful homografting in a rather large animal. A trial with marrow infusion after a single 600 roentgen exposure in the multiple source Cobalt 60 facility at the United States Naval Medical Research Institute, Bethesda, Md., was accordingly undertaken but was not successful.† Therefore, we looked for means other than simple improvement in uniformity of radiation to secure the desired effects.

Several points of possible importance were considered: (1) The animals should be young and healthy and under good veterinary care before and after

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†This experiment was performed in company with Drs. M. Edgerton, D. Jackson, and E. Smith of the Johns Hopkins Medical School, Baltimore, Md.

radiation. (2) The amount of marrow used in the graft infusion should be considerable, 10 to 20 billion nucleated cells. Early restoration of circulating formed elements may well be important in getting the animal through the critical first 2 weeks that immediately follow radiation. (3) The major problem in the dog is probably an active and relatively radiation-resistant immune mechanism. (4) Steps other than single exposure to radiation should, therefore, be taken to impair this mechanism; that is, repeated exposures to radiation,[4] use of ACTH preradiation and postradiation, and splenectomy before radiation. (5) The marrow donor should be genetically close to the recipient, preferably a female sibling or female parent.[3]

With the above factors in mind, an additional series of preliminary experiments was performed.

Experiment A.—Two female dogs, 4 months old, of the beagle persuasion* (Dogs Nos. 4 and 5), were prepared by deworming and immunizing against distemper and hepatitis. After 4 weeks normal health in kennel they were subjected to four 20-minute periods of total body radiation, each consisting of 100 r. measured in air at mid-body with a Victoreen electrometer. To accomplish this, each dog was anesthetized with Nembutal intravenously and confined by a circular retainer in an area 16 inches in diameter, 100 cm. from a G. E. Maximar Unit operating at 250 kv. and 10 Ma. with filters 0.25 mm. tin, 0.4 mm. copper, and 1.0 mm. aluminum, giving a half value layer of 2.2 mm. of copper. The uniformity of radiation in this area had been explored with the Victoreen and was 5 ± 0.5 r. per minute measured in air.† The position of the dog in the retainer was changed at the end of each 20-minute period of exposure: (1) head north, left side up, (2) head south, right side up, (3) head south, left side up, and (4) head north, right side up. Exposure to 400 r. (approximately an $L.D._{50}$ for these animals) was given on each of 3 successive days, total exposure 1,200 r.

When radiation was commenced, the animals were taken off Kennel Ration and Hunt Club Meal and placed on a diet of whole milk and strained liver (Beech-Nut Baby Food preparation). They were also given penicillin, 100,000 units, and streptomycin, 0.25 gram, intramuscularly twice daily, and oxytetracycline, 0.5 gram, intramuscularly.

Immediately following the third day's radiation, one animal received 4 to 5 billion nucleated marrow cells from an unrelated pregnant bitch of the hound persuasion. This marrow was prepared for infusion by suspension in TC 199 and human albumin, and marrow clumps were broken up with a screen syringe.[6]

Both experimental animals died on the sixth day with symptoms typical of acute radiation syndrome: anorexia, loose and slightly bloody stools, pyrexia, and signs of pulmonary infection. Their peripheral blood counts had shown a progressive drop in leukocytes and platelets to a vanishing point on the fifth day as indicated in Fig. 1.

*They look like beagles, but are known not to be purebred or inbred.

†To minimize soft back scatter, the dogs were placed on a base of straw one foot above a floor of concrete. Radiation measurements were also made at this level above the floor.

Experiment B.—Four sibling dogs of the beagle persuasion, about 4 months of age, were similarly kenneled and prepared for study. Spleens were removed from one male and from one female (Fig. 1). Daily administration of ACTH, 10 units intramuscularly twice daily, was begun at the times indicated in the figure. The radiation procedure, time of marrow infusion, and antibiotic and dietary regimens were as described in Experiment A.

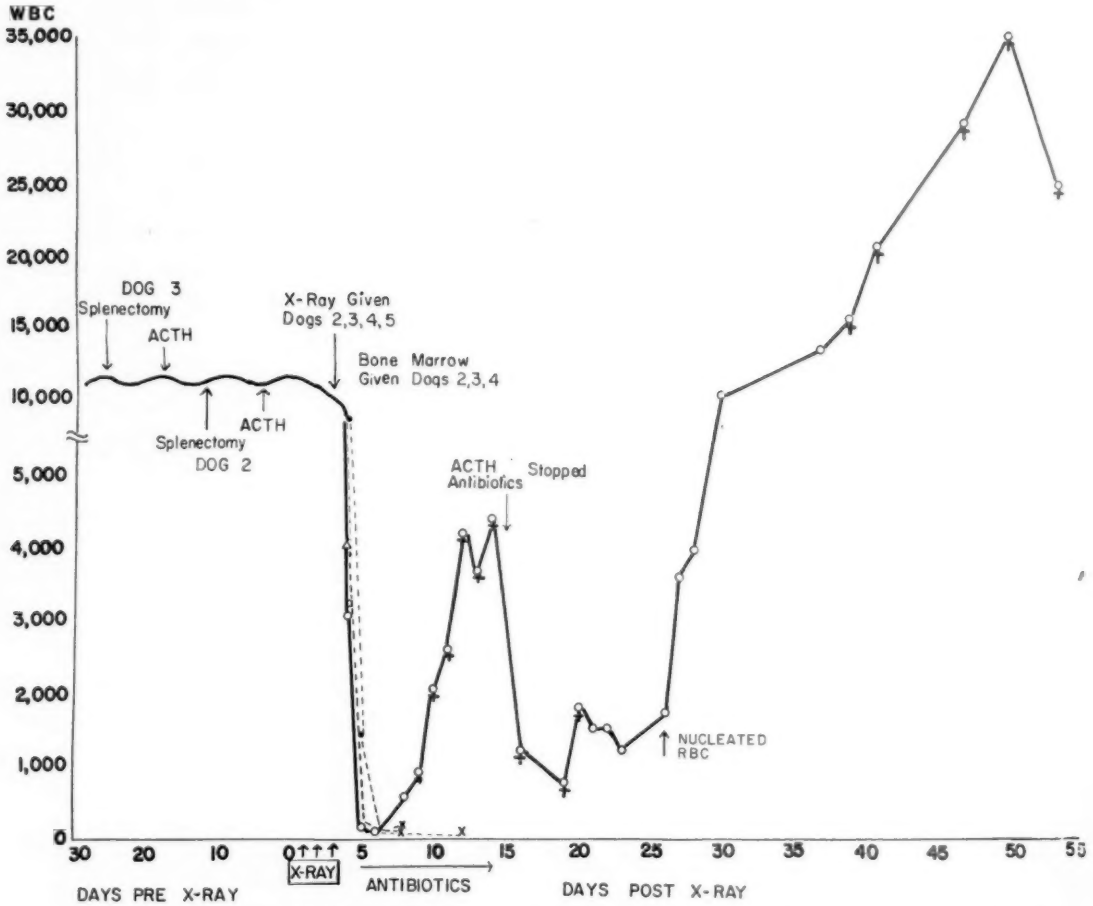

Fig. 1.—Peripheral leukocyte counts following lethal total body radiation and marrow transfusion in the dog. ♀Female type polymorphonuclear cells present in the circulation of male Dog No. 3. The notation "nucleated RBC" denotes a period when immature forms of red blood cells and white blood cells appeared in the peripheral circulation and when, because of immaturity, leukocytes of the female type could not be recognized. The dotted lines stopping on days 6 and 12 represent the course of the white blood counts in Dogs Nos. 4, 5, and 2, respectively.

The splenectomized male (Dog No. 3), a black dog, received 8.6 billion nucleated marrow cells freshly removed from a sister, a white bitch. The marrow of the donor animal had been stimulated by venesection and removal of 50 to 75 ml. of blood every 3 days for a total of 3 times, the last bleeding being 2 days prior to donation of marrow. The splenectomized female (Dog No. 2) received 2 billion nucleated marrow cells from an unrelated male beagle.

Dog No. 2 died on the twelfth day of acute radiation syndrome. Postmortem examination showed consolidating pulmonary hemorrhage and sepsis

(gram negative rods in profusion) as the immediate cause of death. The intestine was not grossly altered except for a ground-glass appearance of the serosa and one small area of fresh hemorrhage low in the ileum. Small scattered areas of erythropoiesis were present in the marrow cavities. The peripheral white blood count is described in the figure.

Dog No. 3, the splenectomized male that received a sizeable dose of marrow from a female sibling, went through the immediate postradiation syndrome satisfactorily. His temperature did rise, and he did show signs of radiation effect: anorexia, vomiting, loose and slightly bloody stools, cough, and signs of pulmonary infection and congestion. In contrast to the other dogs, this illness appeared serious, but not critical. By the fourteenth day, he was eating well of regular kennel fare and had gained one pound ($\frac{1}{10}$ body weight) over his immediate postradiation drop of approximately 2 pounds. His circulating leukocytes had returned to normal number and were showing the approximately 4 per cent female forms[2] typical of his remaining and untreated female sibling.

On the fourteenth day, ACTH and antibiotics were discontinued. Dog No. 3 thereupon had a fever of 106° F. and on the following day was critically ill. The behavior of his peripheral blood leukocyte counts is detailed in the figure.

It was suspected that stopping ACTH and antibiotics had permitted a septic invasion and perhaps a sloughing of his graft. ACTH and antibiotic administration were reinstituted, and a semblance of normal health returned in about 10 days. Mature leukocytes gradually reappeared. They were of female type.

All medication and special dietary treatment was discontinued on the thirtieth day. The dog has remained afebrile and continues to have female type leukocytes in the number usually recognized in normal females (3 to 4 per cent). The continued elevation of the white count, 25,000 total, polymorphonuclears 80 per cent, lymphs 15 per cent, and mononuclear cells 5 per cent, may represent residual infection in an animal deprived of the normal splenic and lymphoid mechanisms of bacterial resistance. However, no physical signs of continued infectious disease are evident and the animal appears essentially normal, though somewhat below the weight and vigor of the normal untreated sibling control (Dog No. 1).

DISCUSSION

In the experiment of Rekers and associates,[5] large amounts of homologous bone marrow were given to irradiated dogs without unequivocal effect upon survival rates. This failure may be interpreted as indicating a residual ability of the host to reject the homograft through immune mechanisms inadequately suppressed by the amount of radiation employed. The amount of radiation used (350 r.) was somewhat below an $L.D._{50}$. In this dosage range in other species,[7] infusion of marrow may actually increase rather than improve the death rate.

From subsequent studies[1] and our own observations, it is known that single exposures in the $L.D._{100}$ range and beyond are not followed by successful marrow homografts in the dog. This species, therefore, illustrates the fact

that simple exposure to lethal radiation is not necessarily accompanied by suppression of immune response sufficient to permit successful homografting.

In the experiments reported here, an effort was made to destroy the immune response of the host by spreading[4] as well as by increasing the dose of radiation. Splenectomy and administration of ACTH were used to decrease further the activity of immune mechanisms. By a summation of these effects and by the use of genetically related donor marrow, a successful and lifesaving graft was obtained.

Studies are in progress to determine the relative importance of the several procedures used. Apropos of the type of marrow may be noted the fact that the successful graft was between siblings and was female into male rather than the reverse.[3] The siblings used were not mongrels in the gross sense, neither were they purebred nor inbred. It would be difficult to term the graft isologous. The donor was white and the recipient black.

In the graft that took, the amount of marrow infused was considerable, 8.6 billion nucleated cells. The splenectomized female (Dog No. 2) received less marrow, 2 billion cells, and received it from an unrelated male animal. Her clinical behavior and the appearance of her marrow spaces at post-mortem examination suggest the possibility that a return of marrow function had been interrupted by intercurrent infection.

SUMMARY

A functioning marrow graft showing female-type leukocytes in the percentage characteristic of normal females has been secured in a male dog. The preradiation, radiation, and postradiation procedures and the reasons for them are outlined and discussed. Barring the possibility of active acquisition of tolerance from unusual and unlikely placental communication during interuterine life, the graft falls in the category of successful postradiation homograft.

We wish to express our gratitude to Michael Jastremski, D.V.M., for his aid in conducting these experiments and to Dr. Charles Ashley, Associate Pathologist of the Mary Imogene Bassett Hospital, for his histologic studies of Dog. No. 2.

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Editorials

CONDUCTED BY I. S. RAVDIN, M.D.

Are We Too Rigid in Our Criteria in Advising Surgery for the Complications of Duodenal Ulcer?

Both the surgeon and internist are in accord that duodenal ulcer disease constitutes primarily a problem necessitating medical management, with surgery being reserved for complications which do not respond to an adequate medical program. It is well appreciated that the majority of individuals with duodenal ulcer may live an otherwise normal existence save for periodic exacerbations of their disease, which are usually controlled with dietary or other conservative measures. Figures from leading medical centers show that surgical intervention is necessary to control duodenal ulcer disease in only 10 to 20 per cent of all cases, with 15 per cent perhaps being a near accurate appraisal.

Perforation as a complication requiring surgery is universally accepted by most surgeons and the mortality following simple ulcer closure has decreased measurably in recent years. Immediate gastric resection in properly selected cases is now gaining increasing popularity and the reported results appear gratifying. The indications for surgery in regard to the other well-known complications are, however, less universally agreed upon. Wide discrepancies in opinion prevail in regard to the circumstances under which a medically treated duodenal ulcer should not longer be treated as such and surgical therapy advised.

Pyloric obstruction, in most instances, is associated with ulcer disease of long duration. A reasonable proportion of these patients receive benefit from nasogastric decompression, but all too frequent the improvement is transient and surgical treatment proves necessary. Many of us have seen patients undergo repeated bouts of pyloric obstruction necessitating prolonged hospitalization and time lost from work before they are transferred to the surgical service.

The same holds true in regard to hemorrhage. The patient who had massive bleeding from a proved duodenal ulcer will in all likelihood, at some time in the future, experience further bleeding, and, unless definite contraindications exist, surgery should be recommended after the initial severe bleeding episode. Age per se should not govern one's decision in advising operation when faced with a patient undergoing massive bleeding.

Pain not responsive to adequate medical treatment is an accepted indication for operation. What factors determine when the patient becomes "refractory" to medical measures are, however, open to wide variation and opinions differ as to when surgery should be recommended. Usually no problem is posed

when one is faced with an otherwise stable individual suffering severe ulcer discomfort not controlled by any type of diet or medication. It is the individual who experiences repeated episodes of discomfort each year, lasting several days to a week at a time, with whom we are concerned. Also, the patient who must forever adhere to a strict dietary regime and forsake many of the pleasures of life to prevent an ulcer flare-up is usually not happy with his situation. In these types of ulcer cases, surgery should be advised more frequently. Extreme care, of course, must be exercised in the selection of patients, and one should be reluctant to offer operation to the patient with psychic and emotional overlay. It is indeed gratifying to see duodenal ulcer patients returning for postoperative visits relieved of ulcer distress for the first time in many years. Many will volunteer the information that they are sorry that they did not have an operation sooner.

It should be emphasized again that duodenal ulcer disease is in essence a medical problem, but surgical indications should be less rigid in certain circumstances. It would appear that possibly 30 per cent of duodenal ulcer patients might, at some time, be suitable candidates for surgical treatment. In advising surgery, one must, of course, seriously consider the morbidity and mortality associated with the procedure if an increasing number of patients are considered for operation. In elective procedures in our leading institutions, the mortality rate should not exceed 0.5 to 1 per cent. Also, the postoperative complications and long-term side effects must be kept at a minimum if an increased number of patients are considered for surgery.

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Blood Volume

One of the greatest needs in American surgery is an accurate and simple method of determining blood volume. It should be possible to make this determination quickly and easily so that the patient's blood volume could be followed during the operative procedure and repeatedly determined during the postoperative period. At present, the surgeon may obtain a blood volume determination before operation but, by and large, during the operation he must depend upon various methods of determining the blood loss. Of these perhaps the most effective has been the weighing of dry sponges so that the weight of blood loss and the measurement of the blood removed from the wound by means of suction can be determined. When the sponges are weighed immediately, before evaporation is allowed to take place, and careful attention is paid to any blood loss on the drapes and other blood which cannot be readily weighed, it is then possible roughly to estimate the blood loss with an accuracy of within

perhaps 10 per cent. This procedure has proved to be fairly satisfactory in most instances except in those patients whose blood is being lost into the intestinal tract or tissues and cannot be calculated. The patient with gastrointestinal hemorrhage has been an outstanding example where the surgeon would be in a much better position to follow the course of events if the blood volume could be determined frequently, accurately, and easily.

Now that cardiac surgery has become commonplace, the need for a simple method for blood volume determination has become even greater. In a good many cardiac conditions the blood volume may be considerably higher than normal. This is true in most patients with a left-to-right shunt such as a patent ductus arteriosus, atrial septal defect, or ventricular septal defect. For many years the surgeon has recognized that if he has a patient with a large patent ductus arteriosus the blood volume may be high and that when the patent ductus arteriosus is obliterated, the need for that high blood volume no longer exists. It has been considered unnecessary, therefore, to replace the blood loss at operation completely. Much additional information is needed, however, as to whether or not the blood volume in such patients should be reduced to normal immediately. This problem has become much more acute in the older patient with an atrial septal defect and in the patient with a ventricular septal defect. One of the most important problems of the team running a heart-lung machine is to see that the patient has the same amount of blood returned to him through the artery as is withdrawn from his venous circulation. With care, this can be and has been carried on with fair accuracy. If the patient's blood volume could be monitored at the same time, however, the surgeon would be in a much more favorable position to calculate necessary blood replacement. At present the surgeon must carefully estimate the amount of blood loss from the patient and machine and replace the blood loss, but he is still in somewhat of a quandary as to whether or not the patient starting out with a high blood volume should be reduced to a normal blood volume during and immediately following the closure of a left-to-right shunt and, if so, the problem of calculation of these factors leaves much to be desired.

In the cardiac surgical patient when the blood pressure falls, the question almost invariably will arise as to whether the patient's blood volume is low, whether peripheral dilatation has inadvertently occurred, or whether there is failure of the myocardium to propel the blood adequately. Although this problem arises almost daily with the cardiac surgeon, it is not always as dramatic as it may occasionally be. Perhaps it would be fitting to describe a case in point.

A patient who was considered to be a relatively good risk, although somewhat older than usual, had had an uneventful mitral commissurotomy. The valve which was originally very tight had been opened widely. The blood pressure, which had been 100 systolic preoperatively, fell to 80 at the time the valve was opened and did not come back to normal. The amount of blood loss had not been great and was estimated to be 350 c.c. for the entire procedure. The question then arose as to whether the low blood pressure was due to the inability of the left ventricle adequately to handle the increased blood flow through the opened mitral valve, whether it was due to a low blood volume,

perhaps exaggerated by the use of diuretics during the immediate preoperative period, or whether it was simply due to unusual peripheral dilatation, allowing pooling in the systemic circulation. In this particular instance when the blood pressure did not respond to a mild vasopressor (Neo-Synephrine), the blood which had been lost at operation was replaced with an initial transfusion of 500 c.c. Over a period of about the next half hour when the blood pressure did not respond again to a mild vasopressor, a second bottle of blood was given slowly. This was a mistake as was demonstrated by the fact that about an hour after the operation was completed, although the patient was still in the operating room, obvious pulmonary edema appeared. At this point a phlebotomy was performed and 1,000 c.c. of blood was removed, so that the patient's blood volume was calculated to be 350 c.c. below that at the start of the operation. A tracheostomy was also performed and positive pressure breathing was used between periods of aspiration. The pulmonary edema was obvious and copious but only slightly pinkish stained. Some Levophed had been administered before the pulmonary edema began in an effiort to try to get the blood pressure up, so that by now the patient's peripheral circulation was so tightly constricted that it was difficult to obtain the blood pressure although the carotid artery pulsations seemed to be about the same as they had been at the time the patient's systolic blood pressure was obtained at 70 or 80. The surgeon then found himself in the embarrassing position of having decreased the blood volume by 1,000 c.c. in order to avoid pulmonary edema and yet in the position of feeling that he should discontinue the Levophed in spite of the low blood pressure, because, in effect, it brought about the same result on the heart and lungs as the high blood volume would since it decreased the peripheral vascular bed. It takes a good bit of courage to stop the vasoconstrictors when the blood pressure is low, especially when the pulmonary edema has largely subsided after removal of 1,000 c.c. of blood. However, it also seemed foolish to increase the speed of the Levophed drip in order to increase the blood pressure for fear of again causing pulmonary edema. In this particular patient, the surgeon elected to stop the vasopressors completely. The pulmonary edema completely disappeared and over a period of several hours the blood pressure gradually came back to normal. This entire episode was stretched out over a period of about 6 hours and was fairly trying on the entire team, including the patient who was awake during much of this period. It seems likely that this episode might have been avoided if the surgeon had been able easily to obtain an accurate estimate of the blood volume. Armed with the knowledge that the patient's blood volume was normal, he might have avoided overtransfusion even in the presence of hypotension.

If a simple and accurate method of monitoring the blood volume does become available, a good bit of experience will be needed in order to use it wisely. The normal blood volume for various individuals in various conditions must be determined, including the capacity of the vascular bed during vasoconstriction and vasodilatation.

Considerable progress has already been made in the determination of blood volume. By means of the use of radioactive isotopes, methods are being

developed which seem likely to permit the surgeon to monitor the blood volume with fair accuracy, but the problem of blood loss at the operating table might still be a factor since the tagged red cells would be lost as well as those that were untagged. Whether the amount of irradiation which would be necessary in the use of radioactive isotopes might conceivably have any influence upon children is difficult to predict at this time or whether some method other than the use of radioactive isotopes which might be equally accurate and much simpler to handle might become available is also unknown. The fact remains that the surgeon is frequently put in the position of wanting to know whether the patient's blood volume is normal, above normal, or below normal. In most instances, he must make an estimate on the basis of the patient's clinical condition or calculations which have occurred during the course of the operative procedure or following it. If some of our young men could solve this perplexing problem, many generations of surgeons will be eternally grateful to them.

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Book Review

CONDUCTED BY J. GARROTT ALLEN, M.D.

Gynecologic Management of Urologic Injuries. Henry C. Falk, Philadelphia, F. A. Davis Company.

This volume is attractively presented. It is printed in a "comfortably" readable-sized type and on excellent quality paper. The table of contents indicates that much of the volume is devoted to vesicovaginal fistula. Some space is assigned to stress incontinence and a limited amount of space to ureteral injuries. The text is built largely from the author's personal experience, which may explain the distribution and nature of material. The title might have been more nearly stated "Urologic Injuries in Association with Gynecological Treatment," for there is no reference to urologic injury as a result of pelvic fractures and traumas of other kinds. There are ample references in each of the chapters. There are approximately a hundred illustrations. These are so well done that the book is well worth its value for these alone. Portions of the text are in outline form which is brief. Other brevity is present—as in the chapter on etiology of vesicovaginal fistula. Four and a half lines are devoted to the damage from radium and x-ray therapy for malignancy. Under the management of the vesicovaginal fistula from malignancy or irradiation therapy, only two paragraphs are on the subject. The content of the paragraphs as such are good, but seem rather short. In Chapter 7 there seems to be some incompleteness. On page 127, the author leaves the reader to guess about the subsequent management of the cystotomy wound after the removal of the catheter. Finally, the section on stress and incontinence has ample discussion, except that not all incontinence is the result of urologic injury.

This book would be a desirable and useful addition to the library of anyone concerned with these problems and especially for those not adequately schooled in the management of urologic injuries.

—H. Close Hesseltine